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and
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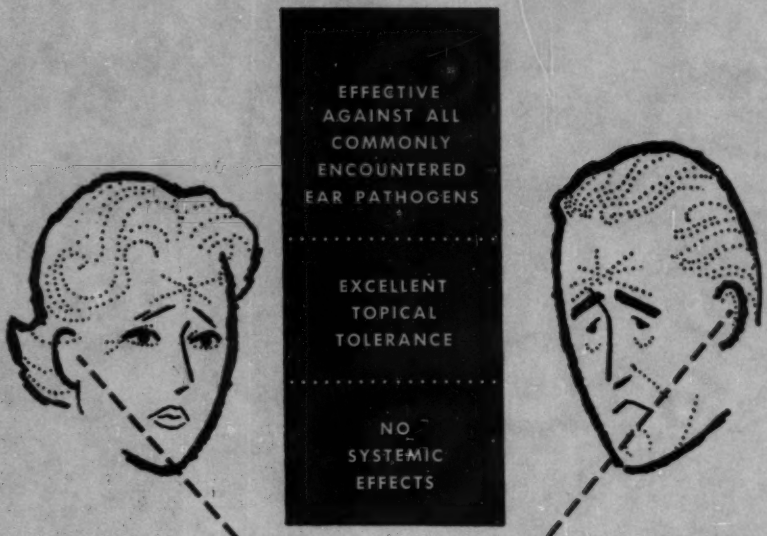

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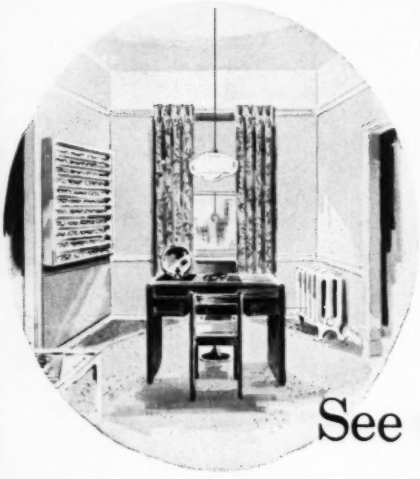

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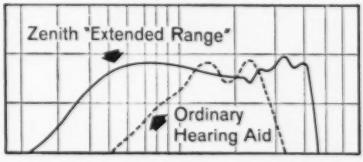

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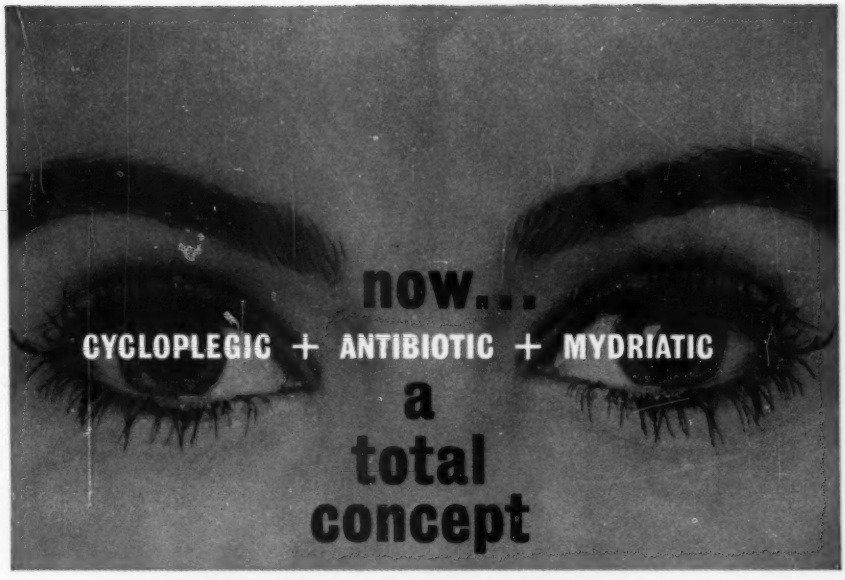

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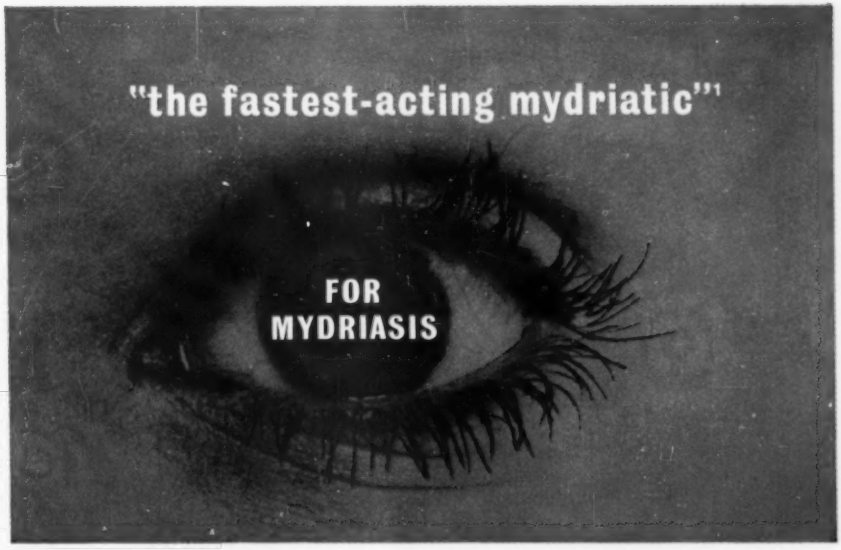

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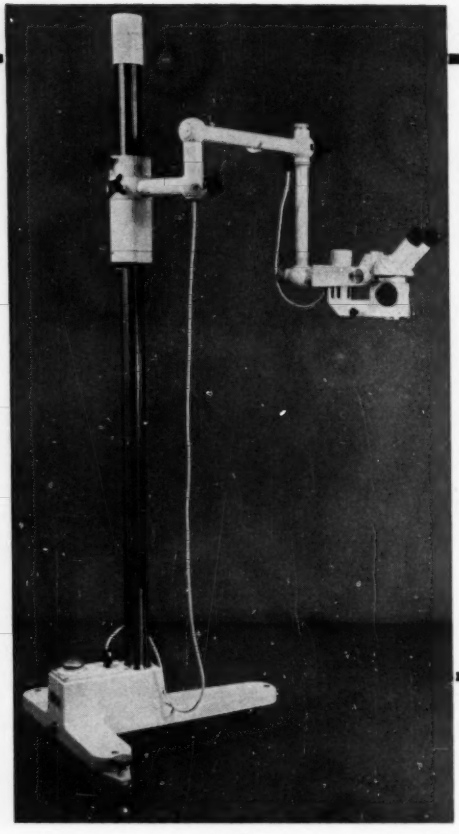

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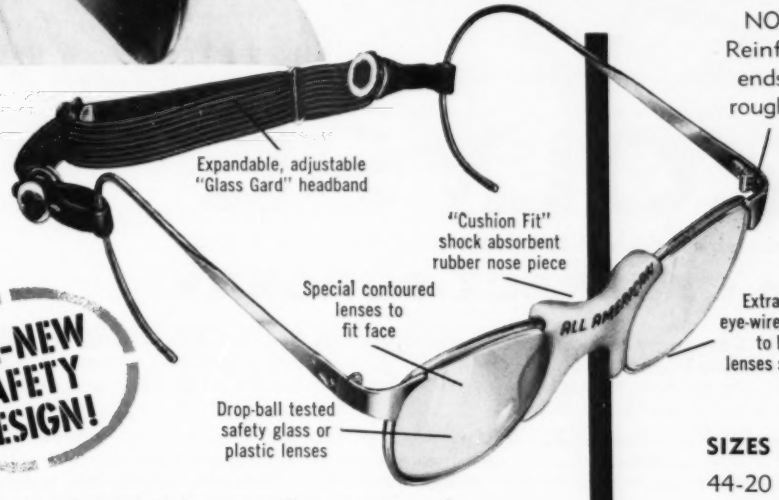
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1 Girard, L. J., Dukes, C. D., and Fleming, T. C. Presented at the International Congress of Ophth., Brussels, Belgium, 1958.
2 Kara, Gerald B., "The Use of Alpha-Chymotrypsin in Cataract Extraction," Research Report No. 10, Alcon Laboratories, Inc., 1959.
3 Vail, D., et. al. Report: Committee on use of alpha-chymotrypsin in ophthalmology. Presented at the Sixty-fourth Annual Session, American Academy of Ophthalmology and Otolaryngology, Chicago, Oct. 11-16, 1959. (To be published)

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This tiny contact lens held feather-light on the tip of a forefinger is a symbol of tremendous significance to those of us in the profession.

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Never before has such a small creation meant so much in the field of sight—or brought so much new beauty in fuller enjoyment of life to so many.

The above photograph represents the finest attributes of craftsmanship, character, and professional skill as exemplified by you. It bespeaks volumes. A 22 inch by 19 inch mat finish print, suitable for framing, of this unusual photo may be ordered from The Plastic Contact Lens Company.

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there's no "fighting" it

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(VINYL ETHER FOR ANESTHESIA, U.S.P.)

Patients rarely fight induction with VINETHENE. Its action is rapid and smooth, seldom causing excitement or nausea. Used prior to maintenance with ether, VINETHENE largely spares the patient from irritation to mucous membranes.

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SUPPLIED: In 10-cc., 25-cc., 50-cc., and 75-cc. bottles, each with adjustable plastic dropper cap.

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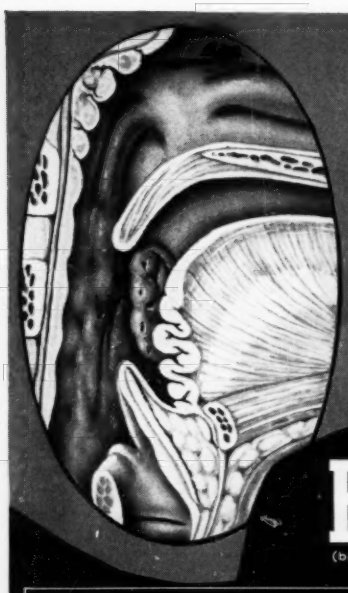

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in treatment of

"CHRONIC SORE THROAT"

often evidenced as chronic tonsillitis, glandular or hypertrophic pharyngitis

. . . without the penalties of antibiotics or sulfonamides

BISTRIMATE®

(bismuth sodium triglycollamate)† Smith

DRAMATIC RESULTS IN CASES RESISTANT TO OTHER THERAPY

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BISTRIMATE—a unique bismuth salt, orally produces therapeutically effective systemic bismuth levels. Use of oral BISTRIMATE is safe, convenient and economical...eliminates injections. **Emergence of antibiotic-resistant pathogens is prevented...with full freedom from antibiotic sensitization.**

DOSAGE: In adults, 1 tablet t.i.d. for 2 or 3 days, then 1 or 2 tablets t.i.d. for a period of 7 to 10 days. In many patients excellent results are often obtained in less than 7 to 10 days.

SUPPLIED: Bottles of 100 and 1000 tablets. Each white scored tablet contains bismuth sodium triglycollamate 410 mg. (equivalent to 75 mg. elemental bismuth).

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1960 COMPREHENSIVE CONTACT LENS SEMINARS

THREE-DAY SEMINARS / LENS ADJUSTMENT SEMINARS

TIME: All seminars will be held from 10 a.m. to 5 p.m. daily.

THREE-DAY SEMINAR: A comprehensive course of study designed to provide information and practical knowledge that can assist you in successfully fitting contact lenses. The latest techniques and developments will be presented such as fitting SPHERCON®, Bi-Curve and Tri-Curve lenses; the use of the new TORCON* lens in fitting unusual astigmia cases; the techniques of fitting BICON®, de Carle, and C. B. bifocal contact lenses; TELECON*, a recently introduced subnormal vision aid; Photo-Electronic-Keratoscopy (PEK*), its theory and use; CONTA-SONICS*, an invaluable aid to the practitioner.

To gain practical experience, each practitioner who registers for this course will receive a personal pair of contact lenses, which will be fitted in class. Your K-readings and Rx must be included with your registration so that your lenses can be processed prior to course date.

ONE-DAY LENS ADJUSTMENT SEMINAR: Provides the basic theory and practice required to perform all contact lens adjustments. This course to include: The CON-LISH* process of uniform edge finishing; methods of applying a CN bevel; grinding, polishing, and blending of intermediate and peripheral curves. The fundamentals of proper lens inspection will be fully demonstrated. Skill in lens inspection will enable you to objectively verify each lens adjustment you make.

SPRING 1960 SCHEDULE OF COMPREHENSIVE SEMINARS

Three-Day Seminars	Lens Adjustment Seminars	City and State	Hotel
February 23-24-25	February 26	Memphis, Tennessee	Peabody
March 1-2-3	March 4	Detroit, Michigan	Statler
March 8-9-10	March 11	Washington, D. C.	Statler
March 15-16-17	March 18	Salt Lake City, Utah	Utah
March 22-23-24	March 25	New York, New York	‡Vision Center
April 5-6-7	April 8	Los Angeles, California	Ambassador
April 12-13-14	April 15	Phoenix, Arizona	Westward Ho
April 19-20-21	April 22	Miami, Florida	McAllister
April 26-27-28	April 29	New Orleans, Louisiana	Jung
May 3-4-5	May 6	St. Louis, Missouri	Coronado
May 10-11-12	May 13	Dallas, Texas	Sheraton
May 24-25-26	May 27	Boston, Massachusetts	Sheraton-Plaza
June 7-8-9	June 10	Montreal, Quebec	Queen Elizabeth
June 14-15-16	June 17	Philadelphia, Pennsylvania	Sheraton
June 21-22-23	June 24	Denver, Colorado	Brown Palace

*Trademark

‡This Seminar will be held at the Wesley/Jessen Contact Lens Company, Vision Building, 635 Madison Ave., New York 22, N.Y.

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Please mail to THE PLASTIC CONTACT LENS COMPANY, 5 South Wabash Avenue, Chicago 3, Illinois. A $25.00 DEPOSIT IS REQUIRED WITH ALL REGISTRATIONS. CHECK THE SEMINAR YOU DESIRE TO ATTEND:

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(Date of Seminar) _____ City _____

Name _____

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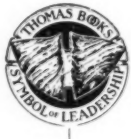
4 New Books for Ophthalmologists

EYE SIGNS IN GENERAL DISEASE

by **F. Herbert Haessler,** *Marquette University School of Medicine, Milwaukee, Wisconsin.* A comprehensive discussion of the some 175 useful eye signs which in many instances first call attention to general disease and often add weight to an otherwise probable diagnosis. The signs are arranged in the order in which they are encountered in the routine physical examination. **Publication date March 1960**

ATOPIC CATARACT

by **Emanuel Rosen,** *Newark Eye and Ear Infirmary.* For the first time under one compendium—an analysis of surgical complications. A suggested therapeutic approach is offered with special emphasis upon pre- and postoperative routine care. Diagnostic signposts are illuminated which will alert the ophthalmologist to better diagnosis. (Amer. Lec. Ophthalmology) **Pub. Dec. '59, 116 pp., 26 il., $5.75**



NIGHT VISION

by **Gaetan E. Jayle** *and* **Albert G. Ourgaud,** *both of Faculte de Medecine de Marseille, France;* **L. F. Baisinger,** *Bakersfield, California; and* **William John Holmes,** *Honolulu, Hawaii.* One of the most outstanding monographs ever to appear in the ophthalmological literature. Covers essential knowledge of night vision under all physical, physiological, technical, and pathological aspects. **Pub. August 1959, 432 pp., 178 il., $13.50**

DISEASES OF THE EYE

by **Eugene Wolff,** *Fifth Edition revised by* **Redmond J. H. Smith,** *University of London.* This volume, now in its Fifth Edition, has proved itself as a sound and popular introduction to ophthalmology, covering the whole field with brevity and clarity. A list of drugs commonly used in ophthalmology and their dosages is a special feature of this new edition. **Publication date April 1960**

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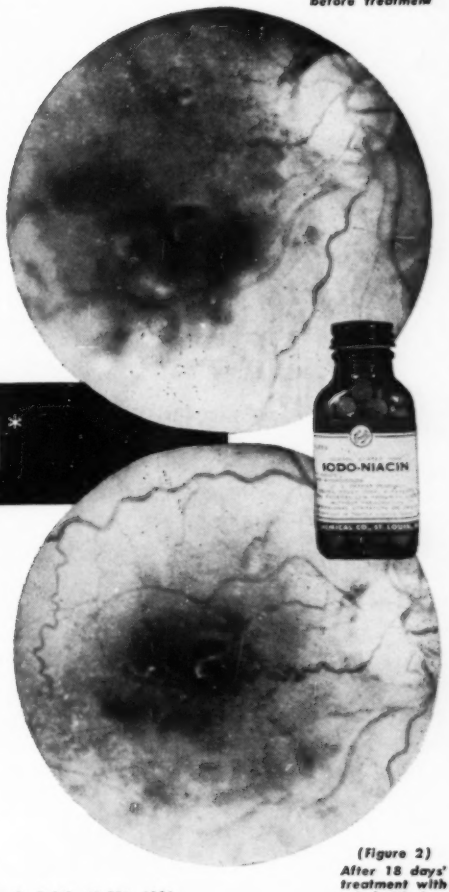
retinal hemorrhages absorbed

with use of

IODO-NIACIN*

(Figure 1)
Retinal hemorrhages before treatment



(Figure 2)
After 18 days' treatment with Iodo-Niacin

As shown by retinal photography, rapid absorption of retinal hemorrhages follows use of IODO-NIACIN. These results have been established in a series of 22 cases, 12 of retinal and 10 of vitreous hemorrhages[1].

IODO-NIACIN Tablets contain potassium iodide 135 mg. (2¼ gr.) and niacinamide hydroiodide 25 mg. (⅜ gr.). The dosage used was 1 tablet three times a day. For greater effect this dosage may be doubled.

IODO-NIACIN may be administered in full dosage for a year or longer without any iodism or ill effect[2].

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1. *Am. J. Ophth.* 42:771, 1956.
2. *Am. J. Digest Dis.* 22:5, 1955.
3. *Med. Times* 84:741, 1956.

*U.S. Patent Pending

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Acute conjunctivitis[1] before treatment, showing engorged irregular superficial vessels

NOW...the true solution for fast anti-inflammatory response and no irritating steroid particles

- mg. for mg. the most active steroid topically—up to 40 times the potency of hydrocortisone
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- superior patient comfort—no stinging, no irritating particles, bland carrier

1. Gordon, D. M.: Scientific Exhibit, American Medical Association, Annual Meeting, San Francisco, 1958.

4 days after treatment ACTUAL CLINICAL PHOTOGRAPHS

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DEXAMETHASONE 21-PHOSPHATE—NEOMYCIN SULFATE

INDICATIONS: Trauma—mechanical, chemical or thermal; conjunctival, corneal, or uveal tract inflammation involving the anterior segment; allergy; blepharitis.

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NeoDECADRON Ophthalmic Ointment (0.05%)—Applied 3-4 times daily.

In severe or sight-threatening conditions, the frequency of administration may be increased. Systemic therapy with DECADRON Tablets may be prescribed adjunctively.

PRECAUTION: Steroid therapy should never be employed in the presence of tuberculosis or herpes simplex.

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Product	Steroid Concentration	active ingredients: Dexamethasone 21-Phosphate (as the disodium salt)	active ingredients: Neomycin Sulfate	Supplied
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DECADRON Phosphate Ophthalmic Solution	0.1%	1 mg./cc.	—	5 cc. (⅙ oz.) sterile dropper-bottles
NeoDECADRON Ophthalmic Ointment	0.05%	0.5 mg./Gm.	5 mg./Gm. (equivalent to 3.5 mg. neomycin base)	3.5 Gm. (⅛ oz.) tubes
DECADRON Phosphate Ophthalmic Ointment	0.05%	0.5 mg./Gm.	—	3.5 Gm. (⅛ oz.) tubes

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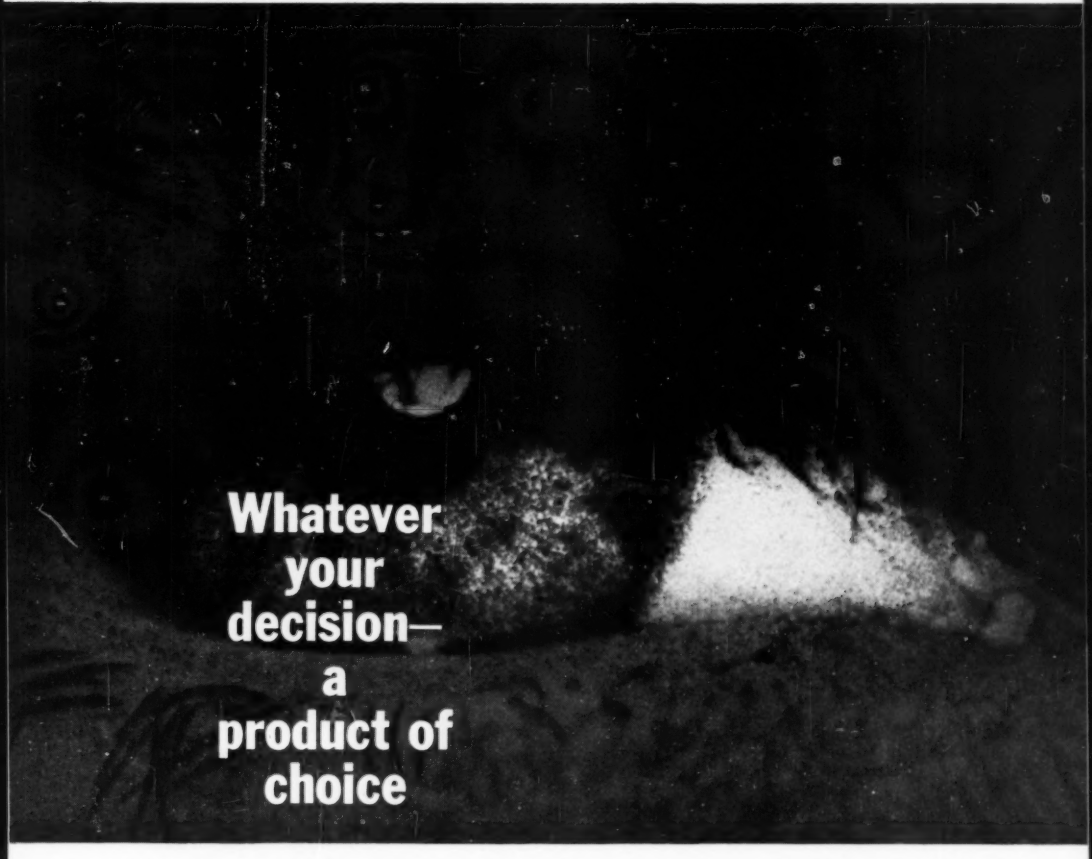

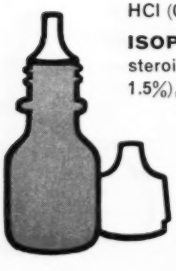

ISOPTO® P-N-P for common, mildly inflammatory, external ocular infections; contains Polymyxin B Sulfate (16,250 units/cc.), Neomycin Sulfate (5 mg./cc.), Phenylephrine HCl (0.12%), and Methylcellulose (0.5%).

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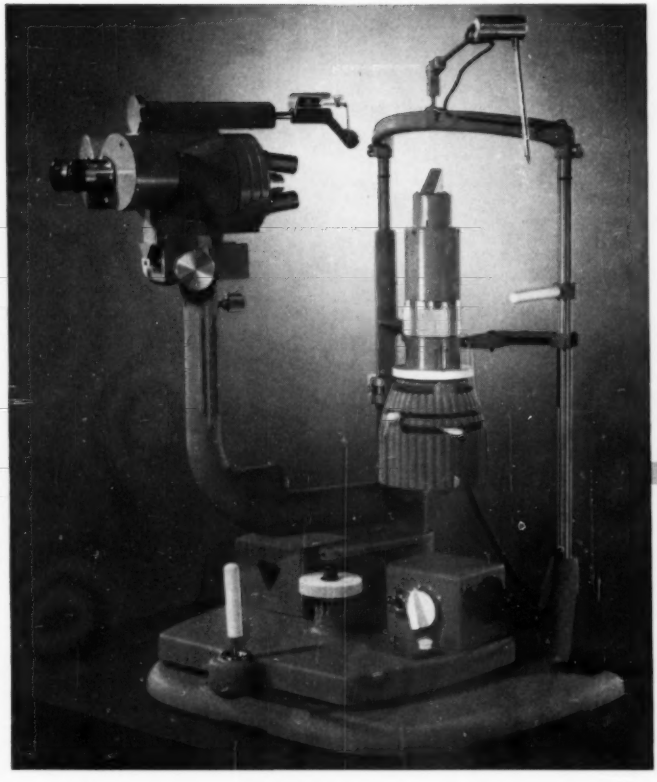

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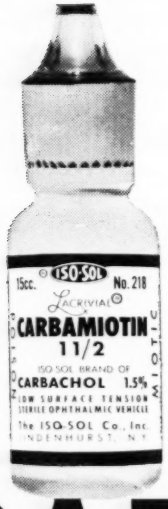

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. . . in chronic non-congestive glaucoma

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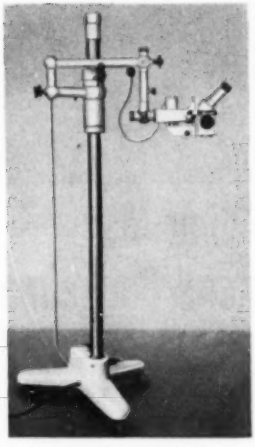

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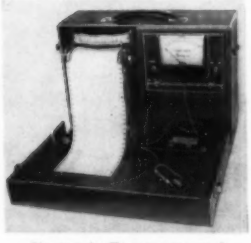

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Telegraph collect if specimen is being sent. Send eyes to . . .

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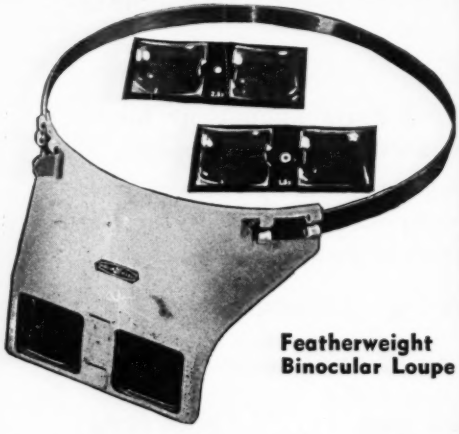
University of California School of Medicine, San Francisco 22



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CASE NO. 1
Blood Coagulation Time 3 min. 15 sec.
Bleeding Time . 1 min. 30 sec.

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Bleeding Time . 1 min. 20 sec.

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Bleeding Time . 1 min. 30 sec.

CASE NO. 4
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All had normal blood studies—yet one had a bleeding problem.

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SALICYLATE

(Brand of carbazochrome salicylate)

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*E. Cheraskin: The Control of Bleeding, J. Am. Dent. Assn., 58:17 (Apr., 1959).

†Extensive bibliography available on request.

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TABLETS—1 and 2.5 mg.
SYRUP—each 5 cc., 2.5 mg.

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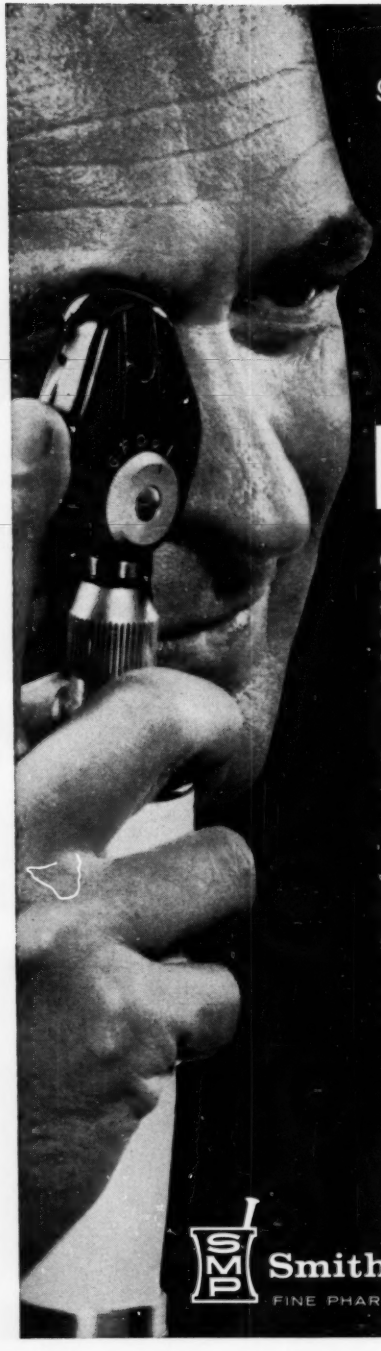

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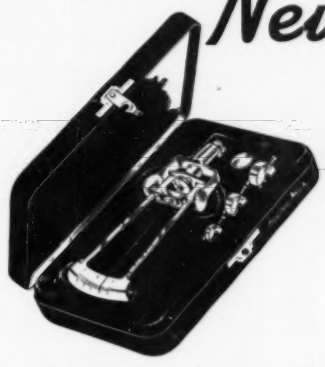

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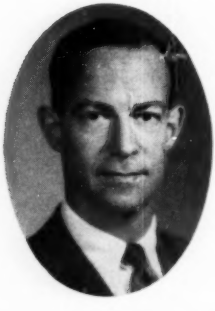

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To be elected President of this Academy is a milestone in anyone's life. I am most grateful to you for having conferred this signal honor upon me. I shall endeavor to maintain the high standard of my predecessors, and I firmly believe that I shall not fail because of the wonderful spirit of cooperation that prevails in this organization. By your willingness to help, you have made this Academy great. You are responsible for its growth and its success. To serve as your presiding officer is both a pleasure and a privilege unequaled in my career. This spirit of cooperation and willingness to help, of course, goes back through the officers and all the members. It was with this thought in mind that I selected "Interdependence," in other words "Teamwork," as the title of my talk.

Fifty-six years ago, when this Academy was formed, medicine was far less complex than it is today. With ever increasing knowledge and greater achievements our profession has long since expanded beyond the scope of any one individual. It has become a cooperative venture between scientist, medical educator and physician in private practice. Each is an integral part of the composite whole, yet the duties and responsibilities of the three groups differ widely.

A few years ago the scientist remained aloof in his laboratory, shielded from the outside world by the abstruseness of his observations. From his ivory tower emerged scientific facts of incalculable value, yet they often fell on deaf ears, for between the scientist and the clinician there was no common ground. Each was distrustful of the other and each pursued his own course with selfish pride, unconcerned with the problems of his fellow worker. Today, this mutual lack of appreciation has largely disappeared and both work together in the solution of difficult medical problems.

As this cooperative spirit has increased, the medical profession has become more and more aware of the real value of research. The scientific side of medicine is receiving its just emphasis, and at long last some funds are becoming available to meet the needs of the investigators. This denotes real progress, yet medical research as it is being conducted needs some revision. To achieve greater results there should be more integration among those engaged in original study. The lone worker, of necessity, must confine his attention to the limited field in which he has had special training. Therefore, his findings lose much of their significance unless they can be correlated with those of others. In the past, scientists have surrounded their projects with great secrecy lest their much desired priority be lost. I am glad to say that these days of distrust are passing, for in many research centers the doors are open to all. In these places there is a willingness among the workers to share their problems.

Presented at the Sixty-Fourth Annual Session of the American Academy of Ophthalmology and Otolaryngology, Oct. 11-16, 1959, Chicago.

They are glad to advise as well as to be advised. Critical analysis of proposed projects is one of the natural outcomes of such discussions. This in itself will not only elevate the standard of research but also will diminish duplication of effort. Unfortunately, one still finds in medical literature the results of ill-conceived and poorly executed experiments parading as scientific facts. I can think of no better way to eliminate these than to encourage greater interchange. Furthermore, much of that precious commodity, manpower, would be saved if scientific activities were more integrated.

At present, little or no concerted effort is being made to correlate the findings of the various groups. Thought has been given to the establishment of a central bureau through which all research projects would be screened. This ideal arrangement is a dream of the future; however, an encouraging step in this direction has been taken by the Bio-Sciences Information Exchange. For the benefit of the scientists, it lists all research projects supported by the National Institutes of Health and several other national agencies. The accessibility of such information should aid in reducing needless repetition of laboratory experiments.

The advances in atomic research during and since World War II testify to the efficiency of concentrated cooperative endeavor, and to the waste produced by duplication of effort. If such interdependent investigations can be carried on for purposes of war, how much more worthwhile if they are used for purposes of health! The story of retrolental fibroplasia is a fascinating example of the value of cooperation between different medical groups. This disease, a product of civilization, was first described by Terry,[4] a clinician and a member of this organization, in 1942. By 1948 it had become recognized as the most common cause of blindness in the preschool child. By that time many of the forces of medical science had been brought to bear on this problem. The relation between prematurity and its development, as suggested by Terry, had been established. Clinical ophthalmologists described and analyzed the appearance and course of the disease, suggested various forms of therapy and speculated upon its etiology. However, it was in the laboratory that the role of oxygen in the development of retrolental fibroplasia was proved. These experimental studies were substantiated by both clinical and research investigations here and abroad. Today, less than twenty years after its recognition, the incidence of retrolental fibroplasia is on the wane. Thus, through the cooperation of ophthalmologist, pediatrician, pathologist, physiologist and embryologist a difficult disease entity was surmounted.

It is most heartening to see that it is now a frequent practice of the embryologist, the biochemist, the physiologist and others interested in basic problems to discuss with clinicians all phases of a disease entity. There are innumerable examples of such interchanges of ideas in our profession. Outstanding among them are the conferences conducted in all branches of medicine under the auspices of various charitable foundations. By cutting across the traditional classifications of the medical disciplines, these closed or limited meetings on urgent medical problems enable scientists and clinicians to become acquainted, exchange ideas, and pool their experience and knowledge. For example, the Josiah K. Macy, Jr., Foundation has instituted a series of such meetings on the subject of glaucoma. These conferences have been held for three days annually for the past five years. They are limited to 25 members and guests selected to represent a multidisciplined approach to this

ocular disease. Although at present the outcome of these assemblies cannot be determined, we can hope that they will do much to clarify the mysteries of this malady. It is to be hoped that in the future even greater emphasis will be placed upon this type of cooperative venture. Such meetings are not only stimulating to both the scientist and the physician in academic medicine, but also are fruitful sources of information for the clinician. Therefore, I urge that their deliberations be more readily available to the profession at large. As the clinician becomes more cognizant of the basic problem, his interest in scientific advancement will be increased and he will begin to feel that, after all, he really is a member of the team.

No one questions that the future solution of many problems in medicine lies in furthering this amalgamation, yet I must remind you that the practice of medicine is not all science. It is rather a delicately balanced fusion of science and art. Peabody has aptly described it as "an art, based to an increasing extent on the medical sciences, but comprising much that still remains outside the realm of any science."[3] As the scientific horizon of medicine has widened, has the art of practice kept pace? It seems to me that as the young giant Science has emerged, the aged Healer has become mired in a morass of abstruse facts. There is no longer keen appreciation of the value of compassion and sympathy in caring for the sick. Let us not forget that "the art of medicine and the science of medicine are not antagonistic but supplementary to each other."[3] The more we know about science, the greater should be our ability to apply the art intelligently. Those in academic life should give serious consideration to this phase of medicine both in their teaching and in their practice, because it will always remain an integral part of our profession. Scientific precision is the watchword of today and there are those who think only in these terms; yet the real physician knows full well that sympathetic understanding is an important supplement to diagnostic acumen.

Failure to accord art an equal place in the limelight of medical progress is responsible for much of the deflection of patients to outside cults. The physician of today, well schooled in scientific methods, is far better equipped to dispel fear than was his poorly trained predecessor, yet I ask, "Is enough attention being directed towards the art of practice in our institutions? Are we not becoming too mechanistic in our approach? Are we not forgetting that reassurance still remains a primary obligation of the physician? Do we emphasize to our students the immeasurable harm that can result from an ill chosen, though scientifically sound, pronouncement?" These questions are pertinent to a discussion of interdependence because, in my opinion, they depict an important flaw in the relationship between medical educators and physicians in private practice. It is the lack of appreciation of the problems of each other that is responsible for the dichotomy that exists between these two groups.

Since the practitioner is a scientist as well as a healer he must have available accurate information on new methods. For this material he has to rely upon those in academic circles. Therefore, if these communications are based upon premature reports of laboratory procedures which have had neither clinical application nor the test of time, much harm can result. In this atomic age when newspapers and periodicals are eager to publish glowing accounts of new medical discoveries, let all of us guard against disclosures of questionable value. When mirrored in the public press, an innocuous-looking scientific article can raise false hopes in the minds of countless thousands. I do decry this fetish for

publicity and firmly believe that if those in responsible positions would assume a more critical attitude, both the practitioner and the public would benefit. The prestige of medicine is in our hands; let us not betray this trust by misleading statements and premature announcements.

The future of medicine is assured. As Atchley[1] has stated, "Medicine as a whole came of age when the stature of the science grew large enough for it to combine with the art in mutual understanding and respect." Yet I agree with Alan Gregg[2] when he said, "For a still more wonderful development of Surgery and Great Medicine as a whole, I would consider the pursuit of knowledge still in its infancy and the scientific method indispensable but not absolute. For there stand compassion, charity and humility as values enduring, essential and with knowledge, wholly satisfying."

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Address of the Guest of Honor

WOMEN AND MEDICINE

GEORGIANA DVORAK THEOBALD, M.D.
OAK PARK, ILLINOIS

IT is an honor for which I am humbly grateful to be chosen Guest of Honor of the American Academy of Ophthalmology and Otolaryngology. It is an honor which, I know, was not conferred upon me alone but upon all women who have practiced medicine throughout the centuries and most especially upon the women who are Fellows of this society.

As an acknowledgment to the pioneering courage of those women in the past who have made the practice of medicine possible for the women of the present, I have chosen to speak this morning on "Women and Medicine."

It has been said that a doctor is born — not made; and is found naturally in both sexes. Moreover, intelligence is not a matter of sex. If it were, would it not be natural for women to possess a greater degree of intelligence, for, as most of you now present know from your study of embryology, the development of the fetus depends upon the infolding of the various crests. Sex is determined by the infoldings of the primary genital crest. If there is one infolding, the child will be male; if there is a second infolding, the child will be female. Embryologically, therefore, a woman has both male and female attributes, which undoubtedly help to explain why, since earliest medical history, there have been records of women practicing the art of healing, although in more recent centuries men were supposed to have the sole prerogative of being physicians.

According to such ancient historians as Euripides, Heroditus and Pliny, whose work has been corroborated by papyri and tablets dating as far back as 3000 B.C., women were the original doctors, the men engaging in the manly pursuits of war and the hunt.

From the time of the earliest medical records, women have been practicing medicine not only as general practitioners and surgeons but also as specialists. As far back as 2730 B.C., a woman was reported to have practiced medicine during the reign of a queen. An ancient Egyptian textbook tells us that women first treated diseases of the abdomen, then diseases of the eye and kidneys, and worm diseases, erysipelas and dropsy. There was a women's college where gynecology and obstetrics were specialties, and there were four volumes of textbooks, one on the eye.

Medicine in Egypt must have been well developed. There were three medical schools: one at On (or Heliopolis), one at Memphis, the third at Sais near the Rosetta mouth of the Nile. Meade quotes an inscription found at Sais which indicates that women were teachers as well as students in medical schools. The inscription reads: "I have come from the women's school at Sais where the divine mothers have taught me how to cure diseases." In her history of *Women in Medicine,* Meade shows a

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picture (dating to 3000 B.C.) which depicts a woman doctor presenting her patients to Isis, thereby curing a boy of poliomyelitis.

Among the women rulers of Egypt who practiced medicine was Cleopatra, whom Aetius praises "for dropping oil into the eyes of newborn babies." Perhaps this is the first record of prophylaxis for ophthalmia neonatorum — and initiated by a woman whom we can honor not as a queen but as a physician.

The renowned school of Heliopolis was located only fifteen miles from Cairo, the ancient On of the Hebrews. It was there that Moses and his wife, Zipporah, and his sister, Miriam, attended medical school.

Greek mythology tells us that the daughters of Aesculapius, Hygeia and Panacea, were famous for their powers to heal. And it is said that Helen of Troy was trained in an Egyptian school, where she obtained a formula for a "drug to lull all pain and anger, and bring forgetfulness of every sorrow."

The Greeks continued to instruct women as well as men. Aristotle and his wife, Pythia, compiled an encyclopedia of biology and physiology, the sections on histology and embryology being the specialty of Pythia. In the first century after Christ, Pliny shared the common opinion that women doctors should be quiet and inconspicuous so that after they were dead no one would know that they had lived.

We all know that no matter how young or old a man is, he needs a mother. And in this connection it is interesting to note the part played by women in ancient Germanic medicine. It was Tacitus who wrote of the ancient Germans, "They take their injuries to their mothers and wives, who do not fear to examine and treat their wounds." Some of these Germanic women physicians, the so-called *pagae,* enjoyed the reputation of possessing supernatural powers.

In 720 A.D., at Hohenburg, Germany, an abbess known both as Odilia and Otilla built a monastery and a hospital which became famous for its cure of eye troubles. It was said that Otilla had been born blind and was cast out to die. Some nuns found her by the roadside and took her to the church for baptism. No sooner did the holy water touch her eyes than her sight was miraculously restored. She became a specialist in eye diseases, as was Saint Lucia of Italy, who, as you may know, is the patron saint of ophthalmology. The legend surrounding Saint Lucia tells us that she refused to renounce her monastic vows to marry the man who had fallen violently in love with the beauty of her eyes. Instead she performed an auto-enucleation, put her eyes on a platter, and sent them to the smitten suitor. The same legend—for legend it surely must be—crops up in Scottish lore, in which another woman, Saint Triduan, is credited with having done the same ghastly thing.

But enough of legend.

To return to history. There are extant thirteenth century pictures showing both nuns and monks removing polypi from the nose and operating on eyes. Dante tells us that in the fourteenth century, the Benedictines, who were medical teachers, felt that, if it were necessary to operate for cataract, they might temporarily adopt the role of barber. And there are records of this same century that a woman physician gave her patients mandrake for pain and with this weed for narcotic even enucleated cataract from the eyes. It is interesting to note, too, that in this same century, "blue stone," the color of the eyes, was used for the ophthalmia which we now know as trachoma.

In Elizabethan England, that is the England of the first Elizabeth, women performed couching operations for cataracts. Indicative of Elizabeth's attitude toward women doctors is an interesting anecdote concerning a skilled herbalist named Margaret Kenwix who was practicing in London without a license. The College of Physicians wished to have her punished. Elizabeth upheld the woman and overruled the College, much to their anger.

In this same century, Anna Maria von Schurman studied medicine in order to find the cure for eye diseases and blindness. Unfortunately, she found no remedies more useful than the age-old one of clay and spittle recommended by Christ.

That at least one woman of the eighteenth century was a competent eye surgeon may be inferred from the following advertisement which appeared in a London newspaper in 1716.

> The Lady Read, in Durham Yard, in the Strand, London, having obtained to a peculiar method of couching cataracts, and curing all diseases of the eyes, by Sir William Read's Method and Medicine, and having had above 15 years experience and a very great Success in Curing Multitudes of Blind and Defective in their sight, particularly several who were born Blind. She may be constantly advised with at her House. . . .

In the eighteenth century there lived in Italy a woman doctor named Anna Manzolini, who, in her assiduous study of anatomy, discovered the correct termination of the oblique muscles of the eye, which, as Gioranini Fantizzi has said, might well have been named for her.

Now to cross the Atlantic and the intervening centuries, we come to women and medicine and the education of women for the practice of medicine in our own time and in our own country.

Women, as well as men, practiced medicine in New England from the first fathers and mothers landed on Plymouth Rock. With the exception of the few who were trained before they crossed the ocean, they were mostly self-educated but, according to historical notes and testimonials on tombstones, some of them were pretty good doctors.

Every pioneer woman was a potential midwife, and those with ability acquired knowledge by reading such medical books as they could come by, and skill by continuous experience in this primal specialty. Their services naturally expanded into general practice, carried on in a neighborly and domestic way. Their opportunities for clinical study and observation were better than those of men, for there were no medical schools in this country during the first 150 years of its history. Before the Revolution, there were very few hospitals.

A young man who wanted to become a doctor started as an apprentice to a practicing physician . . . but such opportunities were not open to women, whose medical services of necessity remained on a neighborly, subprofessional level. There were physicians, however, especially among the Quakers, who taught medicine to women and collaborated with them.

Dr. Harriet K. Hunt (1805-1875) represented the highest type of pioneer physician who practiced medicine without a diploma. From distressing family experiences, she knew that it was right for women to study and practice medicine and that it was wrong to exclude them from medical schools.

Unfortunately, there was nothing she could do about this which would affect her own case. Therefore, with the help of medical books and of qualified physicians, she made the best preparation possible and began the practice of med-

icine in Boston in 1835. She must have been a good doctor. She must have cared about her patients, studied their symptoms and relieved their suffering, for she built up a large practice in a short time. But she craved further knowledge in her chosen field and, being Boston-born, approached Harvard University Medical School. She was repeatedly refused admission, and finally the student body registered moral indignation and passed a couple of resolutions expressing the spirit of the period. We must all smile when today we read the following:

> Resolved: That no woman of true delicacy would be willing in the presence of men to listen to the discussions of the subjects that necessarily come under considerations of the student of medicine.
>
> Resolved: That we object to having the company of any female forced upon us, who is disposed to unsex herself, and to sacrifice her modesty by appearing with men in the medical lecture room.

That settled it! "Sex" was recognized.

Decade after decade, however, Dr. Hunt worked for the advancement of women, enlisting friends and collecting funds for their medical education. In 1878 she made one more attempt to induce Harvard to admit women to its school of medicine. At that time Miss Marion Hovey of Boston offered the sum of $10,000 to the medical school if women were admitted on the same terms as men. This was no inducement. It took about $400,000 to get them into the Johns Hopkins University School of Medicine fifteen years later.

Between 1849 and 1877, however, five medical colleges for women were opened in the United States and one in England.

Another important development of the nineteenth century which went hand in hand with the admission of women to the medical profession on more or less equal status with men was the trickle of women doctors into medical teaching, both in this country and in England. By the beginning of the twentieth century women had come to be accepted as students and practitioners—still seldom on exactly the same terms as men — but rarely as teachers. By the middle of this century, however, the old prejudices and discriminations had been resolved, and today we find women studying, practicing, and teaching on equal terms with men.

On equal terms with men, too, have been the American and English women medical missionaries who have furthered the medical care of peoples in those countries where the treatment of disease has been less than adequate.

In India, for example, the Lady Harding Medical College for Women was founded at Delhi and became one of the most significant institutions in India. The college was opened in 1916 and was staffed successively by women from England and Scotland. It grew to have an enrollment of 100 medical students and a 150-bed hospital.

Dr. Margaret Polk and Dr. Anne Walter Fearn were founders of the first medical college for women in China, at Soochow. Later this hospital was moved to Shanghai, where it became affiliated with the Margaret Williamson Hospital.

These medical women and many of their colleagues have done much to spread the ideal that science has no national boundaries and that the world of medicine is indeed one world.

In the medical disciplines of otolaryngology and ophthalmology, there have been many women in this and other countries who have served their patients well and have brought distinction and honor to our specialties. For them—and for all women who have ever, at any

time in any age, practiced the art of medicine and healing — I thank you for the honor today extended me.

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Report of the Committee on Use of Alpha-chymotrypsin in Ophthalmology

INTRODUCTION

DERRICK VAIL, M.D., *Chairman*
CHICAGO, ILLINOIS

IN the spring of 1957, as most of you know, Joaquin Barraquer, of Barcelona, injected a solution of alpha-chymotrypsin into an eye that had been injured two years before, with the hope that this enzyme would absorb the old blood in the vitreous, present since the injury. Much to his surprise and interest, the lens became completely dislocated. This started him on the study of the use of this substance as an aid to cataract surgery. He performed many experiments on the eyes of animals and of humans whose eyes were blind. Concluding that, so far as he could tell, the enzyme was remarkably effective as a zonulolytic agent and was safe, he used it in routine cases of cataract surgery. On April 8, 1958, he presented his findings before the Royal Academy of Medicine of Barcelona. This represented the first record in the literature of the use of this substance to produce zonulolysis, and to Barraquer must go the credit for its discovery. Since then the attention of ophthalmic surgeons throughout the world has been excited and the material is widely used.

If zonulolysis by this enzyme has solved some questions in the problem of cataract surgery, it has raised many others. The following questions are only a few of those which have been raised: Is the enzyme immediately injurious to the eye in any way? Is wound healing delayed by its use? Are catgut sutures absorbed? Are there delayed injurious effects? Does it increase the facility of cataract surgery? Are there immediate or late complications that are due solely to its use? Does it modify the actual technique of surgery?

In an attempt to solve these pressing problems, at the suggestion of Richard C. Troutman, member of this panel, the Council of the Academy last year established this Committee which reports its findings to you herewith.

A year is obviously too short a time to arrive at all of the answers, and studies on the effect and results of the use of alpha-chymotrypsin, not only in this country but throughout the world, are continuing. However, this interval has permitted the members of the Committee to gather some information of value, as you will see.

Bernard Schwartz and his collaborator will review the biochemistry and pharmacology of alpha-chymotrypsin; Ludwig von Sallmann and his co-workers will discuss experimental studies of some ocular effects of alpha-chymotrypsin; A. Edward Maumenee will report on the effect of alpha-chymotrypsin on the retina (truly a hair curler); Richard C. Troutman will give us the results of an analysis of the factual data contained in a careful study of questionnaires sent to many institutions and ophthalmologists

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in the country, and Bernard Schwartz will conclude with a report of a double-blind therapeutic trial of the effect of alpha-chymotrypsin on the facility of cataract extraction.

At the conclusion of these reports, I shall try to summarize the results of our collective experience in order that you may carry away with you something of reflective value.

A REVIEW OF THE BIOCHEMISTRY AND PHARMACOLOGY OF ALPHA-CHYMOTRYPSIN

BERNARD SCHWARTZ, M.D., PH.D.
and
JOYCE B. SCHWARTZ, PH.D.
BY INVITATION
BROOKLYN, NEW YORK

THE introduction by Barraquer[1,2] of alpha-chymotrypsin for the facilitation of lens extraction has resulted in a widespread use of this substance. As with any other drug used in medicine, a basic knowledge of its structure and actions will enhance its therapeutic success as well as prevent undue complications. It is the purpose of this paper, therefore, to review the biochemistry and pharmacology of alpha-chymotrypsin, selecting such pertinent facts as may apply to its use in ophthalmology.

BIOCHEMISTRY

A. Structure

Chymotrypsin is one of the proteolytic enzymes liberated by the pancreas. The enzyme was first isolated in crystalline form by Kunitz and Northrop in 1933.[20,21] They named it chymotrypsin to denote its clotting action on milk, thus distinguishing it from trypsin, which does not clot milk but does clot blood.

The crystals of alpha-chymotrypsin, as isolated by Kunitz and Northrop,[20] are illustrated in figure 1,B. Although crystallization is a great step forward in purifying an enzyme, it does not by itself indicate pure enzyme.

Chymotrypsin, like other enzymes, is a protein consisting of a number of amino acids joined together by peptide bonds to form chains. The present evidence also indicates that alpha-chymotrypsin consists of three chains of peptides joined together by disulphide linkages.

Measurements of the molecular weight of alpha-chymotrypsin range from 21,600 to 25,000. It exists as a unit of two molecules, or as a dimer, in solution at low pH's and at high concentrations.

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However, in the concentrations and at the pH used clinically, the enzyme exists in solution in a single molecular, or monomer, form.

B. Activation of Chymotrypsinogen to Chymotrypsin

To understand the origin of the qualifier *alpha* in *alpha-chymotrypsin,* it is necessary to review the activation of chymotrypsinogen to form chymotrypsin. Chymotrypsin only exists in the pancreatic cells as an inactive precursor zymogen, called chymotrypsinogen, which is activated to form chymotrypsin by the enzyme trypsin. Two precursors are believed to exist in the pancreas. These are called chymotrypsinogen - α and chymotrypsinogen - β. Both these chymotrypsinogens are distinguished by different isoelectric points and electrophoretic mobilities. Chymotrypsinogen- α (fig. 1,A) is the chymotrypsinogen that produces alpha-chymotrypsin. An outline of the main scheme of the production of alpha-chymotrypsin is shown in figure 2. Chymotrypsinogen - α can be activated rapidly or slowly, depending on the concentration of trypsin added to the chymotrypsinogen. Rapid activation is caused by high concentrations of trypsin, and slow activation occurs with low concentrations of trypsin. Activation of chymotrypsinogen to alpha-chymotrypsin involves the splitting off by trypsin of two dipeptides. Not only is there a release of amino acid peptides from the molecule, but there may also be a rearrangement of the molecule so that intramolecular changes take place.

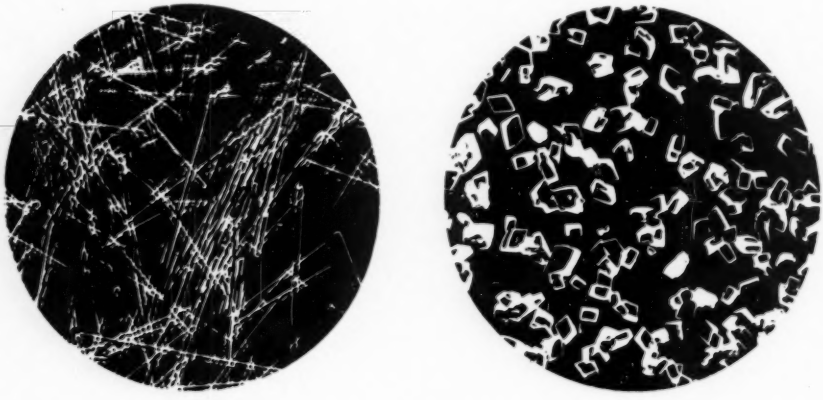
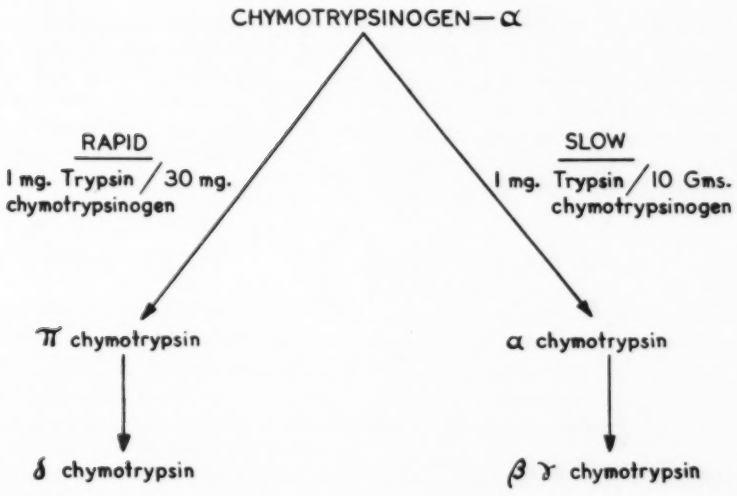


FIG. 1—Crystals of chymotrypsinogen (A) and alpha-chymotrypsin (B). (Taken from Kunitz, M., and Northrop, J. H.[21] by permission of the Rockefeller Institute.)

A number of chymotrypsins can be formed from chymotrypsinogen- α (fig. 2). These differ in their crystalline form, but they all appear to have similar activities enzymatically and to be immunologically the same except for delta-chymotrypsin, which is more active enzymatically than the alpha form. With the rapid activation of chymotrypsinogen- α, π-chymotrypsin is formed. This is a very unstable compound and immediately forms delta-chymotrypsin. With the slow activation of chymotrypsinogen- α, alpha-chymotrypsin is formed: this, in turn, can then go on to form beta and gamma chymotrypsin.



ACTIVATION OF CHYMOTRYPSINOGEN—α TO CHYMOTRYPSINS

FIGURE 2.

C. Production of Alpha-chymotrypsin

Chymotrypsin is usually produced by the method elaborated by Northrop and his colleagues.[27] In this method the ice-cold pancreas is extracted with cold 0.25 normal sulphuric acid. This acid extracts both chymotrypsinogen and trypsinogen, the precursor of trypsin, which is the other main proteolytic enzyme of the pancreas. Chymotrypsinogen is salted out by ammonium sulfate, between 40 and 60 per cent saturation, at pH 5. At this stage traces of crystalline trypsin are added and the chymotrypsinogen is thus converted into alpha-chymotrypsin (fig. 2). By prolonged standing at pH 8, alpha-chymotrypsin can be converted into gamma-chymotrypsin, which can then be filtered off. From the filtrate beta-chymotrypsin can be prepared.

Most commercial preparations of alpha-chymotrypsin are electrophoretically heterogenous at pH 2.4 to 8.6.[9] The heterogeneity is due to contamination with beta-chymotrypsins and gamma-chymotrypsins in the amount of about 9 per cent. The inclusion of beta-chymotrypsin and gamma-chymotrypsin in commercial preparations does not affect the activity of the preparations, since the enzymatic activities of alpha, beta and gamma chymotrypsins are identical.

D. Biochemical Activity

Alpha-chymotrypsin is a proteolytic enzyme. Its main *in vitro* activity is the splitting or hydrolysis of peptide bonds of proteins. As a proteolytic enzyme it is also considered to be an endopeptidase, that is, the enzyme acts in the middle of a peptide chain at various points and does not act solely at the ends of a peptide chain.

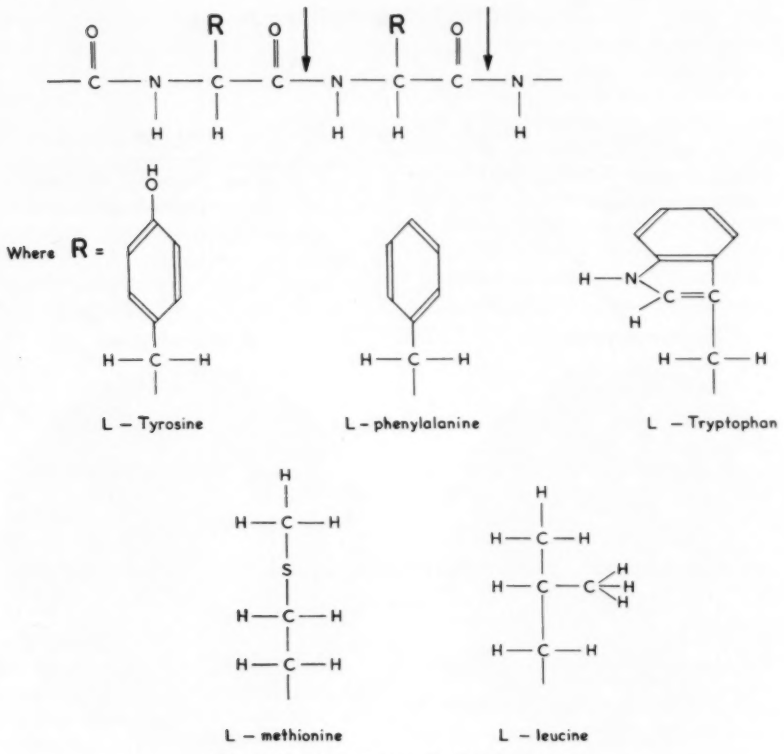


FIG. 3—Proteolytic action of alpha-chymotrypsin.

Alpha-chymotrypsin is distinguished in its hydrolytic activity of peptide bonds from other proteolytic enzymes such as trypsin, by its specificity of action at certain peptide bonds. Thus it will only break those peptide bonds where the amino acid (R) containing the carbonyl group (♂) of the peptide bond is of a certain type, that is, L-tyrosine, L-phenylalanine, L-tryptophan, L-methionine, or L-leucine. This specific action is diagrammed in figure 3, the arrow indicating the site of the peptide bond breakage. The amino acids have been listed above in their order of activity, with L-tyrosine being greater than L-phenylalanine. It appears that the aromatic amino acids containing a benzene ring have greater specificity for activity than the aliphatic amino acids.

Alpha-chymotrypsin can act not only on peptide bonds, but it can also hydrolyze other bonds, such as esters, amides, hydroxyamides, hydrazides, and even carbon carbon bonds. Its esterase as well as its proteolytic activity form the basis for two specific assays of alpha-chymotrypsin. The specification of units for alpha-chymotrypsin is usually based on a test of its proteolytic activity using hemoglobin as the test protein. One unit represents the amount of enzyme which releases one microgram of tyrosine from

denatured hemoglobin. Whether the effectiveness of alpha-chymotrypsin on the facilitation of lens extraction, especially in terms of its zonulytic effect, can be correlated with any specific bond hydrolysis awaits determination.

The optimum pH for the maximum velocity of hydrolysis of protein and synthetic substrates by alpha-chymotrypsin is usually between 7 and 9.

E. Enhancers and Inhibitors of Alpha-chymotrypsin Activity

Calcium has been shown to enhance alpha-chymotrypsin activity.[17,31] Therefore, it is to be expected that dissolving the enzyme in physiologic salt solutions which contain calcium should enhance the activity of the enzyme in the eye. Whether this is a desirable effect remains to be seen for the optimal desired activity is that which causes zonulysis but does not result in other damage to eye structures. However, calcium has the advantage of stabilizing the enzyme so that once in solution, activity will be maintained over at least several hours.[31]

Two groups of compounds are considered to be inhibitors of alpha-chymotrypsin. The first group of substances appears to act by combining directly with the enzyme at its active center, thus inactivating the enzyme. The second group of substances seems to compete with the substrate that normally is attacked by the enzyme. The first group consists of organic phosphorus substances, of which diisopropyl fluorophosphate (DFP) is the best known example. An example of the second group is a series of substituted fatty acids of the general formula $R(CH_2)nCOOH$. Two representatives of this group are beta-phenyl-propionic acid and chloramphenicol.[4,15]

DFP reacts with alpha-chymotrypsin in a stoichiometric ratio, that is, on a mole per mole basis. The maximum inhibitory activity of the DFP coincides with the pH maximum of enzyme activity. The product of DFP with the enzyme is a very stable compound and has been used as a tool to obtain information regarding the active center of the enzyme.

The fact that inhibitors of alpha-chymotrypsin exist leads to the possibility that these substances could be used to counteract the enzyme after the zonulytic action has taken place. This may prove desirable, especially in view of some of the complications reported by Barraquer[3] such as defective wound healing and subconjunctival blebs at the site of the wound. Barraquer[3] has already used beta-phenyl-propionic acid in the anterior chamber after alpha-chymotrypsin in six cases. He has found, however, that this substance did not eliminate the complications which occurred with the use of the enzyme.

Whether chloramphenicol in suitable concentrations could be used as an inhibitor of alpha-chymotrypsin awaits study. The question also arises as to whether preoperative use of chloramphenicol will inhibit alpha-chymotrypsin operatively. Theoretically, a sounder approach to the irreversible inhibition of alpha-chymotrypsin would be to use DFP or some of the newer anticholinesterases such as echothiophate (phospholine) iodide containing an organophosphorous group. The amount of DFP that would be required would be extremely small. Assuming the molecular weight of alpha-chymotrypsin to be 25,000 and the molecular weight of DFP to be 250, and using the dilution of 1 mg. to 5 cc. of alpha-chymotrypsin, since the inhibitory action of DFP to alpha-chymotrypsin is on a mole to mole basis, only 80 micrograms of DFP per 100 cc. would be required. A 0.00008 per

cent solution would be needed, using only 2 cc. of enzyme solution and 5 cc. of the DFP solution for irrigation. At this concentration the possibility exists that the damage DFP would exert in the anterior chamber, including its miotic effect, would be negligible. Provided there is sufficient evidence that the necessity exists for inhibiting alpha-chymotrypsin, research in this area would be especially valuable.

PHARMACOLOGY

A. Experimental

The amount of pharmacologic information available in regard to this substance is relatively small and has only recently been reported. Most of the studies have been involved with its systemic administration. Hendley and his co-workers[13] have compared the toxicity of crystalline trypsin and chymotrypsin in several species, including rabbit, mouse, rat, guinea pig, cat, and dog. In all species chymotrypsin is the less toxic of the two enzymes. The median lethal dose (LD_{50}) for chymotrypsin by rapid intravenous injection ranges from 24,000 units per kilogram in the rabbit to 85,000 units per kilogram in the mouse. In the same study the authors found that chymotrypsin also prolongs the coagulation time and causes hemorrhagic pathologic changes. They indicate that this may be due to its depletory action on blood fibrinogen. Similar findings regarding the clotting time were found by Tagnon, Weinglass and Goodpastor[29] and by Jensen and his colleagues.[18]

Parenteral administration of chymotrypsin also produces a shock syndrome in animals. This indicated by immediate hypotension after administration. The hypotension persists only with relatively large doses.[13,29]

Like trypsin, chymotrypsin has anti-inflammatory activity and has been reported to inhibit the development of experimental egg-white edema in rats,[24] and to increase permeability as measured by intracutaneous dye spreading in rabbits.[6]

Because of its proteolytic action, chymotrypsin has been tried on experimental tumors. However, conflicting results have been obtained.[5,30]

B. Clinical

Chymotrypsin has been tried clinically in areas where trypsin has been used. The enzyme was especially tested in such entities as thrombophlebitis with results similar to those produced by trypsin.[19]

It is interesting to note that Jenkins[16] used systemic chymotrypsin extensively in fifty-one cases of various ophthalmologic entities. These were primarily examples of trauma, the chymotrypsin being used to decrease the pain, swelling and hyphema. Results were variable in cases of uveitis, vitreous hemorrhage and diabetic retinopathy. It is to be noted, however, that in two of the fifty-one cases in which chymotrypsin was used, generalized urticaria developed after a week of treatment.

Similarly, as with the use of alpha-chymotrypsin in experimental tumors, the enzyme has been used clinically in the treatment of cancer. In no case was any beneficial effect reported.[28,30] However, marked side effects were noted with the use of the substance intramuscularly, such as pain and swelling at the site of injection, and in several patients sudden severe reactions with loss of consciousness and peripheral vascular collapse occurred. A definite pronounced allergy to the enzyme developed in some patients; this consisted of urticarial reactions and anaphylactic shock. The side effects of alpha-chymotrypsin, therefore, appear similar to those reported with

the use of trypsin systemically. Whether these allergic reactions will develop locally or systemically in patients who receive the enzyme in cataract surgery, especially after a second procedure, or who have received the enzyme by prior systemic administration is still unknown.

In addition, Fullgrabe[11] has reported the use of chymotrypsin in chronic asthma and in traumatic injuries. Treatment with the enzyme apparently relieved the asthmatic symptoms and hastened the absorption of the traumatic edema and hematomas.

SUMMARY

A selected review of the biochemistry and pharmacology of alpha-chymotrypsin has been presented. Several points that may be of importance in its ophthalmologic applications have been stressed. These are: (1) the possible enhancement and stability of activity to be obtained by diluting the enzyme with physiological salt solutions which contain calcium and the questionable desirability of this effect, (2) the inhibitors of the enzyme such as DFP, beta-phenylpropionic acid and chloramphenicol and their potential use, and (3) the reported development of allergic sensitivity to the enzyme with its systemic administration and the possible development of local ocular sensitivity.

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(Entries 7, 8, 10, 12, 14, 22, 23, 25, 26 and 27 are included as excellent references for review.)

EXPERIMENTAL STUDIES OF SOME OCULAR EFFECTS OF ALPHA-CHYMOTRYPSIN

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OUR chairman suggested that in the cooperative effort of this report three aspects of the alpha-chymotrypsin problem should be studied experimentally in the Ophthalmology Branch of the National Institute of Neurological Diseases and Blindness (NINDB). These were the effect of the enzyme on the corneal endothelium, immunologic phenomena in chymotrypsin-sensitized animals, and changes of the ultrafine structure of the zonula following local administration of the proteinase.

Histologic and cytologic examinations of the corneal endothelium were carried out on rabbits and comprised the greatest number of experiments in these studies. Drs. Shoch and Van Wien, of the Department of Ophthalmology, Northwestern University Medical School, examined histologic sections of enzyme-treated and control eyes. Mr. Caravaggio and I used a new technique of whole flat mounts of the endothelium to investigate cytologic changes and to compare them with those seen in sections of celloidin-imbedded material. Manifestation of the enzyme's antigenicity was examined in preliminary experiments by Dr. van Alphen of NINDB. The electromicroscopic work planned by Dr. T. Wanko of our group was deferred, since Dr. Ake Holmberg and his co-workers[8] at Washington University in St. Louis had already reported the results of experiments on monkeys before our material was processed. With the permission of the St. Louis investigators, their findings will be mentioned in the present report.

EFFECTS ON THE CORNEAL ENDOTHELIUM

In view of clinical observations to be described later in the conference, studies of the endothelium are of practical interest.

Methods

The Spanish product Quimotrase, in a dilution of 1:5000, and the Armour preparation Alpha Chymar, 750 Armour units diluted with 5 ml. of 0.9 per cent sodium chloride solution, were introduced into the anterior or posterior chamber of rabbits by different techniques. Drs. Shoch and Petzinger slowly irrigated the anterior or posterior chamber for three minutes with the enzyme solution, using a blunt needle which was introduced through a keratome incision and was attached to a Fuchs' syringe, allowing simultaneous withdrawal of the infused material. Washing with 1 ml. of saline solution followed the injection of the enzyme. Anesthesia was obtained with 0.5 per cent tetracaine hydrochloride applied topically and retrobulbar injection of 2 per cent xylocaine. The second eye of each animal was treated similarly but with saline solution alone. In Dr. Schoch's series, the eyes of 24

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rabbits were examined histologically at time periods varying from one hour to two weeks. The anterior segments of an additional 12 eyes were fixed in Carnoy solution and sent to the NIH laboratories for cytologic examination. These animals were killed at intervals of 2 hours, or 1, 3, 7, 21 and 42 days after the injections.

In the NINDB series the administration of the enzyme was varied in order to provide for a uniform exposure of the endothelium to the proteinase. A modified tear-sac cannula was introduced through a small Graefe-knife incision from behind the limbus, into the anterior chamber, and through the pupil into the posterior chamber. The excess fluid escaped by way of the limbal wound. In the second technique, the tips of two 27-gauge needles were placed into the chamber angle. One of the needles was connected to a microsyringe and the other served as the out-flow channel. Finally, to avoid the effect of turbulence of the fluid on the endothelial lining, one needle attached to a three-way stopcock was inserted into the anterior chamber. The aqueous humor was slowly aspirated and replaced with the chymotrypsin solution. After three minutes this fluid was withdrawn and the anterior chamber was briefly filled twice with 0.9 per cent sodium chloride solution. Twenty-four animals were used in this series, but three were excluded from further studies because of technical mishaps. For the initial surgery in short-term experiments, Nembutal anesthesia alone was used. For long-term experiments, the systemic anesthesia was supplemented by ophthaine instillation and retrobulbar injection of 0.5 ml. of 2 per cent xylocaine.

In view of the known limitations of histologic studies of the corneal endothelium in sections, a new technique was devised in our laboratory for preparing flat mounts of the entire endothelium after the Feulgen reaction was completed. Descemet's membrane and the endothelium were separated from the stroma after fixation and staining. This was accomplished by blunt dissection of the excised cornea under a stereomicroscope. Radial incisions made it possible to flatten the Descemet's membrane-endothelium preparations and to mount them in gelatine (fig. 1). The mitotic index of the normal endothelium of young adult rabbits was determined in such mounts. Mitotic counts and cytologic changes were recorded in the same way on the material from experimental and control eyes.

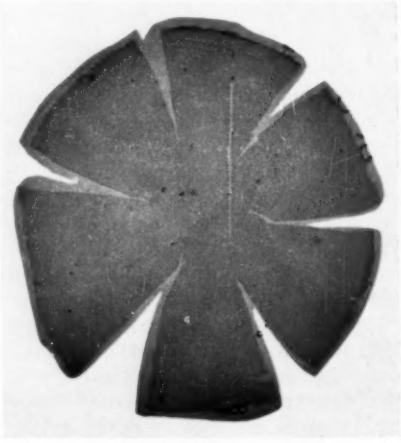

FIG. 1—Flat mount of the entire corneal endothelium of the rabbit following the Feulgen reaction.

Results

The regular biomicroscopic examinations of the NIH chymotrypsin series showed clear corneas in the majority of animals, and in these, except for the presence of fibrin clots, the anterior chambers were normal. In other experiments, signs of irritation, such as flare

and cells in the aqueous humor and iris hyperemia developed postoperatively. The corneas appeared diffusely gray, or circumscribed parts of the cornea became cloudy and thickened. In several instances, such signs of damage occurred when sodium chloride solution alone had been infused. These changes were observed most frequently when a second needle was inserted through the limbus to permit outflow. When these lesions were confined to a relatively small area, clear throughout, but 4 developed partial and sometimes extensive opacities. In three chymotrypsin-treated animals the corneas became moderately ectatic at the site of circumscribed corneal edema (fig. 2).

The prolonged injection procedure then resulted in corneal damage in about the same percentage of enzyme-treated and of control eyes. It is not known whether this effect was caused by the turbulence of the anterior chamber fluid

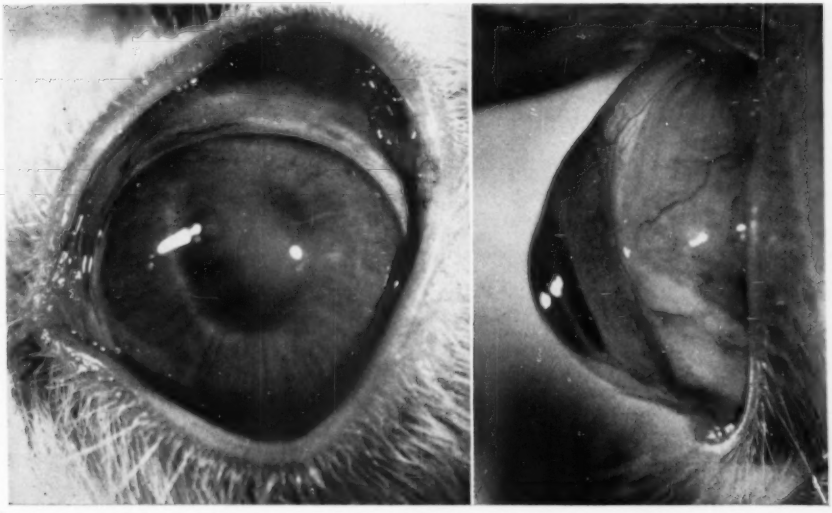

FIG. 2—Partial clouding and slight ectasia of the rabbit cornea 24 hours after treatment with alpha-chymotrypsin solution, replaced after three minutes with 0.9 per cent sodium chloride solution.

they regressed after 24 hours and, as a rule, disappeared after 48 hours. However, extensive corneal opacification persisted for a period of observations lasting about five weeks. At later stages, 12 of 17 enzyme-treated eyes were of normal transparency. The remaining 5 eyes showed various degrees of corneal clouding and signs of irritation. Eight corneas of the controls treated with 0.9 per cent solution of sodium chloride remained during the perfusion or by toxic properties of the physiologic saline solution acting on the endothelial cells, which have been demonstrated on rabbit endothelial cells in tissue culture work reported by Harper and Pomerat.[7]

Dr. Van Wien, pathologist at Northwestern Medical School, summarized the results of the histologic examination of the cornea of 24 animals by stating

that in no case was he able to find any evidence of damage and, without previous knowledge, had been unable to differentiate at any time the eyes treated with enzyme from those treated with the saline solution. Histologic studies of the cornea of the NIH series were in general agreement with this observation, but eyes with clinically visible corneal opacities showed severe edema of the stroma and patchy gaps in the endothelial lining.

The examination of whole flat mounts of the endothelium were planned, first, to establish the mitotic index in the normal cornea of adult rabbits. The population of this cell layer was ascertained using a technique similar to that described for cell counts in the lens epithelium.[12] The average of the calculated figures obtained on 4 animals was 750,000 cells per cornea, which is surprisingly close to the total number of cells estimated in the lens epithelium of the same species. The mitotic counts ranged in five experiments from 7 to 32, with an average of 15 dividing cells per preparation, or an index of 2/100,000 cells. Twenty-four hours following the enzyme treatment or later, the number of cells in mitosis were in excess of this average in 8 of 13 eyes, and surpassed 100 per preparation in 6 of these 8 instances, reaching counts of 280 mitoses. Greatly increased mitotic activity was observed most often at the 24-hour or the 48-hour interval (fig. 3). It did not necessarily show a correlation with corneal edema which could be detected by biomicroscopy. In the control eyes injected with physiologic sodium chloride solution, one of the diffusely clouded corneas showed a rise of the mitotic cell count to 515 cells. In another similar preparation the figure was 91. The counts were moderately increased in 9 of the 11 control eyes when compared to the normal average. Simple paracentesis had no noticeable effect on the cell division in the endothelium 12, 24 or 48 hours after the operation (4 experiments).

The cytologic signs of an injurious effect of the enzyme, and, less frequently, of the infusion of an 0.9 per cent sodium chloride solution, consisted of a disarrangement of the normal endothelial mosaic with gaps between the cells. Occasionally polymorphonuclear leukocytes were found among or on the surface of the endothelial cells (fig. 3). Cells in this area varied in size and often contained pyknotic nuclei. In some areas the prevalence of dividing cells was striking, but abnormal mitotic figures were rare (fig. 4). This picture, then, resembles the phase of endothelial regeneration observed by Nagano[10] after chemical and mechanical injury to the cornea. His findings were confirmed by Binder and Binder,[3] and in experiments in the NIH laboratories. Examination of later stages of the enzyme-treated eyes indicated that the corneal endothelium returned to a normal state several weeks after the injury and cell division decreased to a normal level.

These cytologic studies on the corneal endothelium were confined to rabbits. Efforts to use cat or monkey corneas failed because, with the method employed, Descemet's membrane could not be separated from the stroma in these species.

IMMUNOLOGIC STUDIES

Certain phases of the antigenicity of the enzyme were investigated by Dr. van Alphen in guinea pigs in order (1) to learn about the risks involved in removing the lens of the second eye by zonulolysis after the enzyme had been used in the first eye, and (2) to foresee and prevent harmful effects on patients who

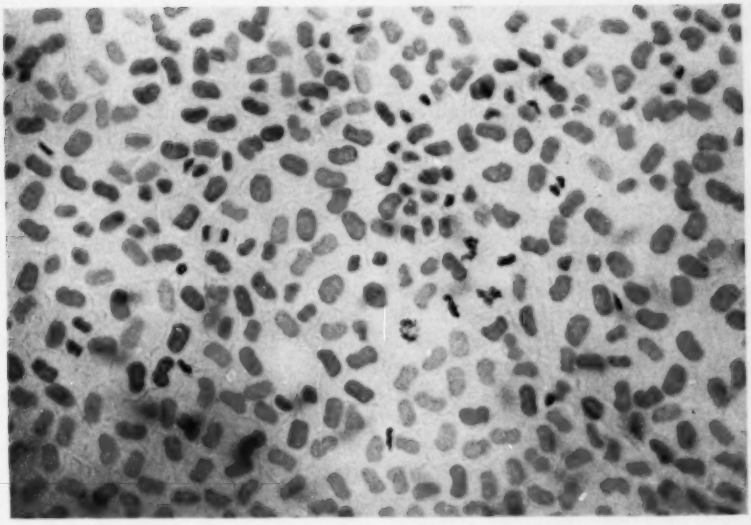

FIG. 3—Disarrangement of the endothelial pattern with gaps between the cells and various signs of cell degeneration. A great number of dividing cells are scattered among the abnormal endothelial cells (48 hours after treatment with alpha-chymotrypsin, magnification 380×).

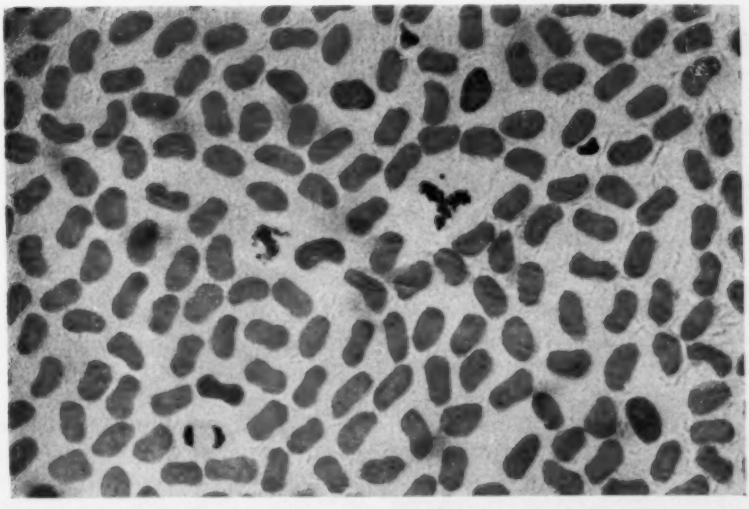

FIG. 4—Tripartite cell division in an area of increased mitotic activity 24 hours after treatment with alpha-chymotrypsin, magnification 600×.

had been treated previously with alpha-chymotrypsin for a variety of systemic diseases. Dr. van Alphen immunized 6 guinea pigs with alpha-chymotrypsin by repeated injections of the preparation in the footpad and subcutaneously under the skin of the neck. A dose of 1 mg., homogenized in Freund adjuvants, was administered eight times at 10-day intervals. Precipitating antibodies were demonstrated with the agar-diffusion technique after five injections with antigen dilution as high as 1:10,000. Unexpectedly, skin testing did not result in a delayed sensitivity reaction except for the highest dose of 1 mg. antigen per 1.2 ml. of saline solution. One month following the sensitization procedure a challenging dose of this concentration was administered by instillation in the conjunctival sac or by injecting 0.2 ml. under the conjunctiva, in the anterior chamber or in the vitreous. No matter what route of administration was selected, no reaction was detected biomicroscopically during an observation time of one month.

ELECTRON MICROSCOPIC

ELECTRON MICROSCOPIC STUDIES OF ZONULOLYSIS WITH THE ENZYME

Electron microscopic examinations of the zonula of monkeys after treatment with alpha-chymotrypsin were reported by Albert P. Ley, Ake Holmberg, and Tsuyoshi Yamashita.[8] From this work it was obvious that in the monkey the enzyme caused a breaking up of the zonular membranes by a process of uniform fragmentation which followed stretching and thinning of the microfibers within three to five minutes. This was clearly documented in the electron micrograph presented with their paper.

COMMENT

The discrepancy of some of the results of histologic examinations reported by Shoch and Van Wien and those recorded in the laboratories of NINDB can be explained by the differences in techniques. It is possible that the turbulence of the infusate was greater with the two-needle technique and that the contact of the endothelium with the enzyme was more uniform when the anterior chamber was filled with the enzyme solution. The mechanism of the clinically and histologically observed corneal injury was not clear but a direct injury by the needle or needles can be excluded because the corneal lesions were distant from the location of the needle tips.

The elaboration of a technique for whole mounts of the corneal endothelium provided new information on the basic problem of regeneration of this cell layer. Cogan[5] pointed out at the session of the Academy in 1950 that the method and rate of endothelial growth are wholly obscured, since mitoses are never seen in the normal endothelium. The early work of E. Ballowitz,[1] Fuks[6] and Nagano[10] failed to demonstrate mitotic cells in the endothelium under normal conditions. Binder and Binder[3] concluded from the examination of fixed, flat-mounted portions of the endothelium of adult rabbits that physiologic regeneration in this cell layer takes place by amitosis. On the basis of our material no issue can be taken as to whether or not amitosis occurs *in vivo* and plays as important a part as it is assumed to play in cells grown in tissue culture.[9] In the present study it was merely shown that the concept of absence of karyokinesis in the normal corneal endothelium in young adult animals is erroneous, and that there is no need to resort to the doubtful mechanism of amitotic cell division to explain the normal regeneration of this cell layer. It is noteworthy that the mitotic index in the endothelium approached that of the pre-equatorial zone of the lens epithelium and that it steeply increased in response to damage as it did in the lens.

In the enzyme experiments, the high mitotic activity of the endothelium was observed in areas where disruption of the regular cell pattern and signs of of cell degeneration were well developed. These cell changes were seen also in control eyes treated with physiologic sodium chloride solution, but there it was less frequent and less extensive. It was concluded from the experiments on rabbits that the corneal endothelium was frequently injured by being in contact with the enzyme and the subsequently introduced saline solution. In about a third of the experiments this damage resulted in corneal clouding. In these instances, large defects of the endothelium could be demonstrated microscopically. Nothing is known about the regeneration of the endothelium in the aged human eye. The results derived from experiments in young, healthy animals, therefore, can only serve as a guideline for observations on the human eye. In general, the changes were of transient nature. It was improbable that a specific enzymatic action was the cause of the lesion.

The immunologic studies on guinea pigs, conducted by Dr. van Alphen, represented a short series of experiments. However, the lack of an adverse effect when a relatively high challenging dose of the enzyme was injected into the anterior chamber or the vitreous of the animals, which had been sensitized for months with the proteinase and had developed a high serum titer of precipitating antibodies, was an important observation. These results indicated that untoward immunologic responses were unlikely to occur if the second eye of a patient was subjected to zonulolysis after the enzyme had been used on the first eye. Previous investigators have reported allergic reactions produced by other forms of administration of alpha-chymotrypsin.[4,11,13]

The conclusion of Bedrossian[2] that the enzyme does not disrupt the zonule fibers but merely weakens them was contradicted by electron microscopic studies of the St. Louis investigators, who documented the breaking up of the zonule fibrils in monkeys.[8] Light microscopic examinations in the laboratories of NINDB, not reported in this paper, also pointed to the fragmentation of the zonule fibers in rabbits.

SUMMARY

1. Alpha-chymotrypsin infused into the anterior chamber of rabbits for three minutes and removed by irrigation with 0.9 per cent sodium chloride solution or the infusion of the sodium chloride solution alone for the same length of time frequently produces damage of the endothelial lining, as seen biomicroscopicaly and in flat mounts. Partial or diffuse corneal opacity can follow the treatment and is often associated with defects in the endothelial layer. If the injury is limited to a circumscribed area, it appears to be transient. Diffuse corneal clouding persisting for weeks occurs when the damage is extensive. Cytologically, mitotic activity is greatly increased and cell degeneration is widespread around the damaged area.

2. In the normal corneal endothelium of the adult rabbit, karyokinesis can be observed. The average mitotic index is 15 dividing cells per whole mount. Regeneration under physiologic or pathologic conditions seems to be accomplished by mitotic cell division.

3. In guinea pigs sensitized to alpha-chymotrypsin the injection of a challenging dose into the anterior chamber or the vitreous does not produce noticeable allergic responses.

4. Electron microscopic and histologic studies provide evidence that the enzyme acts on the zonule with fragmentation of the fibers.

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EFFECT OF ALPHA-CHYMOTRYPSIN ON THE RETINA

A. EDWARD MAUMENEE, M.D.
BALTIMORE, MARYLAND

WHEN the Committee on the Use of Alpha-chymotrypsin was formed at the meeting of this society in 1958, it was charged with the responsibility to investigate the clinical reaction to the irrigation of the anterior and posterior chambers of the eye with alpha-chymotrypsin and it was requested to investigate, experimentally, the effect of this drug on all tissues of the eye. Doctor Stephen Kuffler, of the Wilmer Ophthalmological Institute, had been using alpha-chymotrypsin for several years in his studies on the neurophysiology of the retina. He found that the supporting structure of the retina offered sufficient resistance to fine glass microelectrodes to make it difficult to pass them through the retina into single ganglion cells or nerve fibers. If the retina was irrigated with alpha-chymotrypsin, however, it became "softened" and the electrodes could penetrate the tissue with ease. For this reason, it was decided to inject alpha-chymotrypsin into the vitreous of rabbits to see if it had a detrimental effect on the retinal tissues.

One tenth of a cubic centimeter of 1/5000 dilution (15 units) of alpha-chymotrypsin was injected into the vitreous through a 27-gauge needle inserted very tangentially through the sclera, choroid, and retina.

Most of the injected material remained in the eye after the needle was withdrawn. Twenty eyes were so treated, and ten eyes were similarly injected with the diluent that is used to prepare this enzyme.

There was very little difference between the immediate reaction of the control eyes and the eyes injected with alpha-chymotrypsin. During the first twenty-four hours there was a mild irritation of the eye and a few opacities could be seen in the vitreous in the area of the injection. Occasionally a small choroidal hemorrhage occurred at the site of the needle puncture in both control and treated eyes. The eyes injected with alpha-chymotrypsin occasionally developed a few more vitreous opacities and small retinal hemorrhages away from the site of the injection. In approximately one third of the eyes, the lens became subluxated or dislocated into the vitreous on the second to fourth day after injection.

The eyes were removed on the fifth to fourteenth day after injection and studied histologically. In only one instance was there evidence of a spontaneous detachment of the retina, but in approximately three fourth of the eyes there was a marked disruption of the normal retinal architecture. This ranged from an apparent breakdown of the normal supporting fibers of the retina with a scrambling of the various neural elements to an almost complete atrophy of the retina (figs. 1-4). The severity of the reaction did not appear to be related to the time interval between the injection and enucleation when the eyes were

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From the Wilmer Ophthalmological Institute, Johns Hopkins Hospital and University, Baltimore 5.

Presented at the Sixty-Fourth Annual Session of the American Academy of Ophthalmology and Otolaryngology, Oct. 11-16, 1959, Chicago.

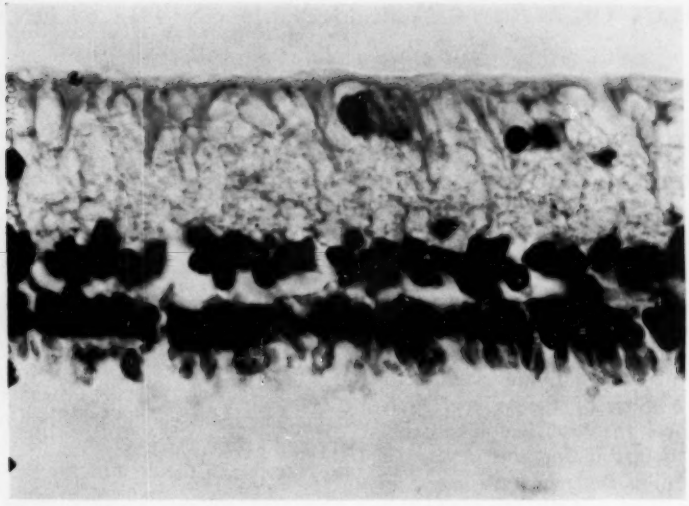

FIG. 1—Normal rabbit retina stained with hematoxylin-eosin on the opposite side of the retina from that injected with alpha-chymotrypsin. (Note Müller's fibers.)

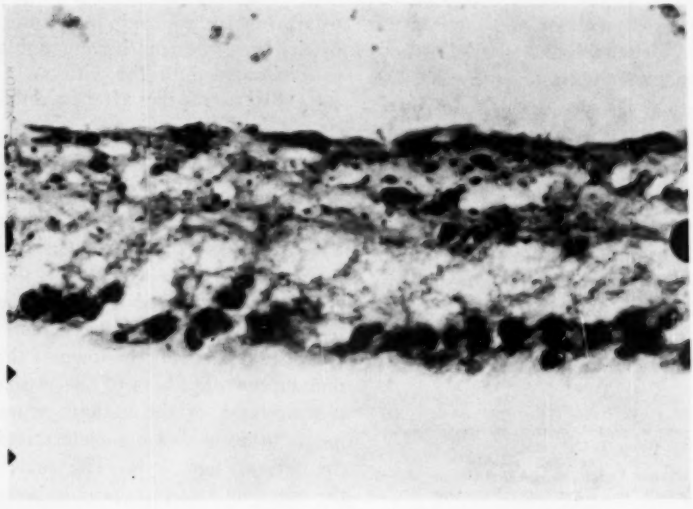

FIGURE 2.

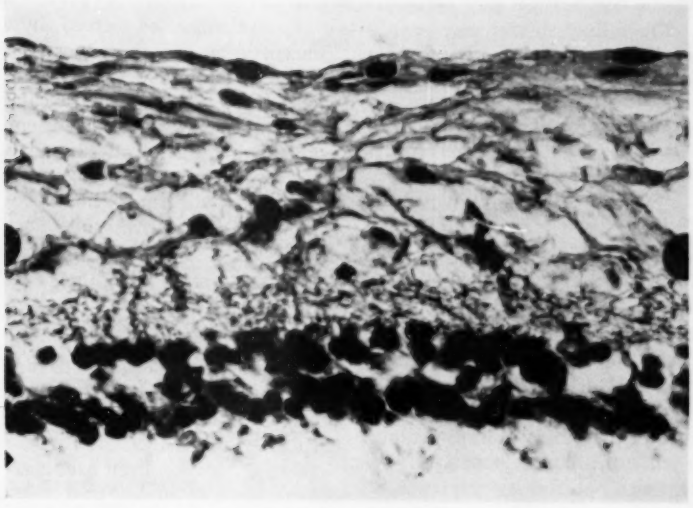

FIGURE 3.

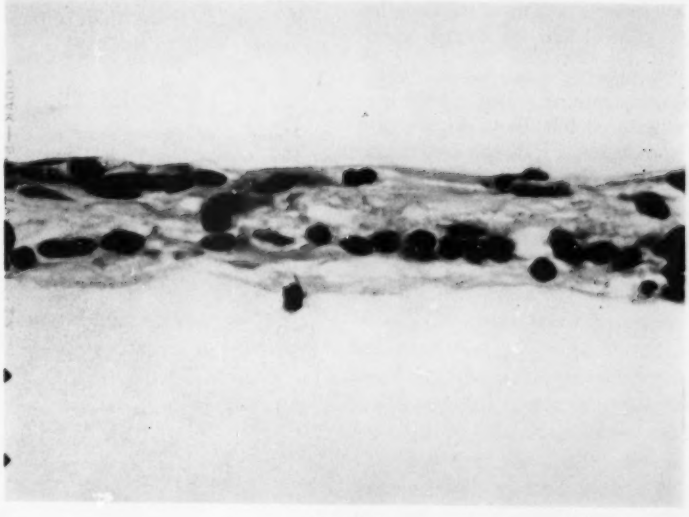

FIGURE 4.

FIGS. 2, 3 and 4—Various stages of degeneration of the fibers of the retina.

removed five to fourteen days after injection. The retinal disturbance usually appeared to be limited to one side of the eye; on the opposite side, it retained its normal architecture.

None of the animals were blinded after the injection of alpha-chymotrypsin, for all showed a normal pupillary reaction to light.

The retina from an eye that had been enucleated because of a recent traumatic destruction of the globe and the retina from an eye that had been obtained at autopsy six hours after death were divided; one half of the retina from each eye was placed in normal saline solution and the other half in a solution containing 150 units of alpha-chymotrypsin per cubic centimeter. After twenty minutes the tissues were removed from these solutions and processed for histologic examination in the routine manner. Microscopic examination of these specimens which had been stained with hematoxylin-eosin revealed no difference between the control and the treated specimens.

These observations are of a very preliminary nature, but they do warrant several comments. First, the concentration of alpha-chymotrypsin and the duration of exposure to which these retinas were subjected exceed, by far, the concentration and the exposure that the human retina would receive were alpha-chymotrypsin to be used for cataract extraction. Next, it does not seem unreasonable that the retina should be damaged by this enzyme, for the material has proteolytic and fibrolytic action which will probably disrupt most tissues of the body if they are exposed to its action for a long enough period of time.

It is interesting to note, however, that the supporting structure of the retina appears to be more sensitive to the enzyme than the neural cells, medullated nerve fibers and blood vessels. This might be explained by the fact that the suspensory ligaments of the lens (zonular fibers) are thought to arise from the anterior portion of the retina during embryonic development.[1] It is, therefore, theoretically possible that the supporting structure of the retina may have a sensitivity to this enzyme that is more comparable to the zonular fibers than to mesodermal structures such as the iris.

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NATIONAL SURVEY ON THE FACILITY OF CATARACT EXTRACTION, OPERATIVE AND IMMEDIATE POSTOPERATIVE COMPLICATIONS

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NEW YORK, NEW YORK

A STATISTICAL study of a large number of cataract cases in which the enzyme was used is desirable in order to determine its effects on the human eye.

Questionnaires were prepared and tested. When a satisfactory questionnaire had been evolved (table I), it was sent together with a supply of the enzyme and directions for its use to qualified investigators. More than 1,800 questionnaires were returned. This represented the work of 151 institutions and more than 200 ophthalmologists. These questionnaires were checked, and a final total of 1,581 were judged sufficiently accurate to have their data transferred to IBM cards for analysis. This method provided us with a large series of cases in a short period of time (six months). The Committee wishes to thank the ophthalmologists for their participation in this survey, without which this report would have been impossible.

RESULTS AND DISCUSSION

Approximately one third of the total 1,581 cases were classified as "ideal" (table II). In these cases all preoperative complications, both ocular and systemic, were recorded as negative. These patients also had had no previous use of the enzyme. These groups were further divided into age groups, 0 to 49 years and fifty years plus. The numbers in the under 20 years age group were insufficient to be analyzed separately.

Does alpha-chymotrypsin facilitate lens extraction (table III)?

On the basis of subjective evidence, the surgeons felt that in the total series, extraction of the lens was not facilitated in 13 per cent of cases. However, only 8 per cent of the surgeons felt that in the "ideal" series, their extraction was not easier (table IV).

On the basis of objective evidence, the percentage of extracapsular extraction in all cases done with alpha-chymotrypsin was determined as 7 per cent. Comparing this percentage to that in the series of Owens and Hughes,[1] in which over 2,000 cases were analyzed, it will be noted that 19 per cent cataract extractions reported were extracapsular. It was suspected that this figure might be high, as the operations were performed nearly fifteen years ago and many advances have been made in lens extraction technique and instrumentation since that time. Therefore, in the enzyme series first eyes operated upon without

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Supported by research grants from the National Society for the Prevention of Blindness, Enzytrase, Inc., Armour Pharmaceutical Company and Trubek Foundation.

Presented at the Sixty-Fourth Annual Session of the American Academy of Ophthalmology and Otolaryngology, Oct. 11-16, 1959, Chicago.

TABLE I

DO NOT FILL IN

Date Received _____

Assigned Study No. _____

AMERICAN ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

COMMITTEE ON ALPHA-CHYMOTRYPSIN
Chairman - Dr. Derrick Vail

ALPHA-CHYMOTRYPSIN QUESTIONNAIRE

INSTRUCTIONS :
1. Please mark individual boxes with red pencil as indicated in sample below.
2. Mark only one number in each column not marked PMP. Columns designated PMP indicate that more than one number may be used. One or more numbers should be used in all boxes.
3. Return to : Dr. Richard C. Troutman, Division of Ophthalmology
State University of New York, Downstate Medical Center
450 Clarkson Avenue, Brooklyn 3, N. Y.

SAMPLE

Column 10
AGE
0. Less than 10
1. 10-19
2. 20-29
3. 30-39
4. 40-49
5. 50-59
6. 60-69
7. 70-79
8. 80-89
9. 90 and over
Y. Unknown

5

Column 42
IMMEDIATE POST-OPERATIVE COMPLICATIONS
(1-21 days) (6) PMP

1 3

0. None listed below
1. Uveitis, moderate
2. Uveitis, severe
3. Corneal edema or striate keratitis
4. Endophthalmitis
5. Suture failure without wound rupture
6. Iris prolapse
7. Choroidal detachment without delayed reformation of anterior chamber

Patient's Initials _____ Hospital No. _____ Date of Operation _____

Referring Doctor _____ Referring Hospital _____

CHECK ONE :- ☐ Attending Surgeon ☐ Resident

Columns 1-3 (For office use only)

Columns 4-7 (For office use only)

Column 8 SEX
1. Male
2. Female

Column 9 RACE
1. White
2. Negro
3. Oriental
4. Other (Specify)
Y. Unknown

Column 10 AGE
0. Less than 10
1. 10-19
2. 20-29
3. 30-39
4. 40-49
5. 50-59
6. 60-69
7. 70-79
8. 80-89
9. 90 and over
Y. Unknown

Column 11 PREVIOUS CATARACT SURGERY IN OTHER EYE

0. None listed below
1. Intracapsular extraction
2. Extracapsular extraction

Column 12 PREVIOUS CATARACT SURGERY IN OTHER EYE COMPLICATIONS (1) PMP

0. None listed below
1. Hyphema
2. Wound re-opening with uveal or vitreous prolapse
3. Wound re-opening without uveal or vitreous prolapse
4. Anterior chamber shallow or absent
5. Iris prolapse
6. Uveitis
7. Corneal opacity
8. Striate keratitis
9. Vitreous loss
X. Secondary glaucoma
Y. Retinal separation

Column 13 PREVIOUS CATARACT SURGERY IN OTHER EYE COMPLICATIONS (2) PMP

0. None
1. Endophthalmitis
2. Epithelial downgrowth
3. Vitreous in anterior chamber
4. Papillitis
5. Optic atrophy
6. Enucleation
7. Post-operative inflammatory iris adhesions
8. Sympathetic ophthalmia
9. Other (Specify)
Y. Unknown

Column 14 CATARACT TYPE IN OPERATIVE EYE

1. Congenital mature
2. Congenital immature
3. Adult mature
4. Adult immature
5. Traumatic mature
6. Traumatic immature
7. Clear lens
8. Other (Specify)

Column 15 PREOPERATIVE COMPLICATED FACTORS IN OPERATED EYE

(1) PMP

0. None
1. Synechia posterior
2. Anterior uveitis, active
3. Anterior uveitis, inactive
4. Posterior uveitis, active
5. Posterior uveitis, inactive
6. Chronic open angle glaucoma, controlled
7. Chronic open angle glaucoma, uncontrolled
8. Closed angle glaucoma, controlled
9. Closed angle glaucoma, uncontrolled
X. Retinal separation
Y. Dislocated lens

Column 16 PREOPERATIVE COMPLICATING FACTORS IN OPERATED EYE

(2) PMP

0. None
1. Cornealendothelial dystrophy
2. Corneal dystrophy, other (Specify)
3. Corneal opacity secondary to ulceration
4. Corneal opacity secondary to trauma
5. Myopia
6. Previous glaucoma surgery, external filtering type
7. Previous glaucoma surgery, endocular type
8. Malignant glaucoma
9. Previous retinal separation surgery
Y. Other (Specify)

Column 17 OTHER CONCURRENT MEDICAL DIAGNOSES PMP

0. None
1. Diabetes
2. Hypertension
3. Arteriosclerotic heart disease
4. Blood dyscrasia
5. Other (Specify)
Y. Unknown

Column 18 HISTORY OF ALLERGY OR HYPERSENSITIVITY PMP

0. None
1. Hives or urticaria
2. Angioneurotic edema
3. Food allergy
4. Drug allergy
5. Contact dermititis
6. Hay fever
7. Asthma
Y. Unknown

Column 19 PREVIOUS USE OF ENZYME PMP

0. None
1. Trypsin (Tryptar, Parenzyme)
2. Chymotrypsin (Chymar, Enzeon)
3. Alpha-Chymotrypsin in other eye for cataract surgery
Y. Unknown

Column 20 ANESTHESIA PMP

1. General with intubation
2. General without intubation
3. General with muscle relaxant
4. Local

Column 21 ADEQUACY OF ANESTHESIA PRE-OPERATIVE MEDICATION

1. Adequate
2. Inadequate
Y. Unknown

Column 22

OPERATIVE TECHNIQUE - SECTION

1. Graefe Knife
2. Keratome and scissors
3. Other (Specify)
Y. Unknown

Column 23 OPERATIVE TECHNIQUE - FLAP
0. None
1. Fornix
2. Limbal
Y. Unknown

Column 24 OPERATIVE TECHNIQUE EXTRACTION
0. Spontaneous delivery
1. Forceps
2. Erisophake
3. Loop or spoon
Y. Unknown

Column 25 OPERATIVE TECHNIQUE - IRIS
0. None
1. Peripheral iridectomy
2. Complete iridectomy
3. Peripheral iridotomy
4. Radial iridotomy
5. Iridodialysis

Column 26 OPERATIVE TECHNIQUE - SUTURES
0. None used
1. Preplaced silk
2. Preplaced catgut
3. Postplaced silk
4. Postplaced catgut
5. Tract, silk
6. Tract, catgut
Y. Unknown

Column 27 SITE OF SUTURES
0. None used
1. Corneal-Scleral
2. Corneal-Corneal
3. Scleral
Y. Unknown

Column 28 NUMBER OF SUTURES
0. None
1. One
2. Two
3. Three
4. Four
5. Five
6. Six
7. Seven
8. Eight
9. Nine
X. Ten or more
Y. Unknown

Column 29 POST-OPERATIVE MANAGEMENT OF IRIS
0. Nothing
1. Dilate
2. Constrict
Y. Unknown

Column 30 CHYMOTRYPSIN
0. None
1. Pevya 1:5,000
2. Pevya 1:10,000
3. Armour 1:5,000
4. Armour 1:10,000
5. Other (Specify)

Column 31 AMOUNT OF CHYMOTRYPSIN
0. None
1. Less than 1 c.c.
2. 1 to 2 c.c.
3. 2 to 5 c.c.
4. More than 5 c.c.

Column 32 CHYMOTRYPSIN - TIME IN SOLUTION BEFORE USE
0. None
1. Less than 15 minutes
2. 15 to 29 minutes
3. 30 to 59 minutes
4. 1 to 3 hours
5. 3 to 6 hours
6. More than 6 hours

Column 33 TIME IN ANTERIOR CHAMBER BEFORE LAVAGE WITH SALINE AND APPLICATION OF EXTRACTION INSTRUMENT
0. Less than 1 minute
1. 1 to 2 minutes
2. 2 minutes
3. 2 to 3 minutes
4. 3 to 4 minutes
5. 4 to 5 minutes
6. 5 to 9 minutes
7. 10 to 15 minutes
8. More than 15 minutes

Column 34 ADDITIONAL CHYMOTRYPSIN USED
0. No
1. Yes
If yes, amount (no. of c.c.) _____
Time interval in anterior chamber _____

Column 35 FACILITY OF CATARACT EXTRACTION ON THE BASIS OF PREVIOUS EXPERIENCE
1. Easier
2. Not easier

Column 36 OPERATIVE COMPLICATIONS PMP
0. None
1. Loss of formed vitreous
2. Loss of fluid vitreous
3. Presentation of vitreous without loss
4. Rupture of lens capsule
5. Posterior dislocation of lens
6. Hemorrhage
X. Before extraction instrument applied
Y. After extraction instrument applied

Column 37 IMMEDIATE POST-OPERATIVE COMPLICATIONS (1-21 days)

(1) HYPHEMA

0. None
1. Hyphema, minimal
2. Hyphema, moderate
3. Hyphema, maximal

Column 38 IMMEDIATE POST-OPERATIVE COMPLICATIONS (1-21 days)

(2) HYPHEMA

0. None
1. Absorbed spontaneously, less than 4 days
2. " " 4 to 6 days
3. " " 7 to 9 days
4. " " 9 to 21 days
5. No absorption after 21 days

Column 39 IMMEDIATE POST-OPERATIVE COMPLICATIONS (1-21 days)

(3) ABSENT OR SHALLOW ANTERIOR CHAMBER

0. None
1. In less than 5 days
2. 5th to 7th day
3. In more than 7 days

Column 40 IMMEDIATE POST-OPERATIVE COMPLICATIONS (1-21 days)

(4) ABSENT OR SHALLOW ANTERIOR CHAMBER

0. None
1. Spontaneous reformation
2. Surgical therapy
3. Medical therapy

Column 41 IMMEDIATE POST-OPERATIVE COMPLICATIONS (1-21 days)

(5) WOUND RE-OPENING

0. None
1. In less than 3 days
2. 3rd to 6th day
3. 7th to 9th day
4. 10th to 14th day
5. 15th to 21st day

Column 42 IMMEDIATE POST-OPERATIVE COMPLICATIONS (1-21 days)

(6) PMP

0. None listed below
1. Uveitis, moderate
2. Uveitis, severe
3. Corneal edema or striate keratitis
4. Endophthalmitis
5. Suture failure without wound rupture
6. Iris prolapse
7. Choroidal detachment without delayed reformation of anterior chamber

Column 43 SUTURE REMOVAL

0. In less than 14 days
1. 14 to 21 days
2. In more than 21 days
3. Not removed (silk)
4. Not removed (catgut)

TABLE II
POPULATION DATA

POPULATION	TOTAL	AGE GROUP	
		0-49	50+
All cases	1581	369	1212
Ideal cases*	588	107	481

*Ideal case: no preoperative complications, ocular or systemic, no previous use of enzyme.

TABLE III
FACILITATION OF CATARACT EXTRACTION

	ALL CASES		IDEAL CASES	
	NO.	%	NO.	%
Easier	1327	87	536	92
Not easier	206	13	44	8

TABLE IV

PERCENTAGE OF CATARACT OPERATIONS RESULTING IN EXTRACAPSULAR EXTRACTION

TYPE OF CASE	PERCENTAGE		
	TOTAL	AGE GROUP 0-49	AGE GROUP 50+
All cases	7		
First eye without alpha-chymotrypsin	17	31	14
Second eye with alpha-chymotrypsin	6	6	6
Owens & Hughes	19		

alpha-chymotrypsin were compared with second eyes operated with alpha-chymotrypsin. In the first eyes operated upon without alpha-chymotrypsin, 17 per cent of the operations were reported as extracapsular extractions. In the second eyes in which alpha-chymotrypsin was used, 6 per cent of the operations were reported as extracapsular extractions. On the basis of these data, alpha-chymotrypsin not only facilitates cataract extraction but also reduces the percentage of extracapsular extractions.

Since alpha-chymotrypsin does reduce the percentage of extracapsular extractions, then is 1:10,000 *as effective as* 1:5,000 *dilution (table V)?*

There appears to be no large difference between the effect of the 1:5,000 and 1:10,000 dilutions, extracapsular extractions being reported in approximately the same percentages in each concentration in each age group.

If alpha-chymotrypsin facilitates cataract extraction and reduces the percentage of extracapsular extractions using either of the suggested dilutions, then what are the major operative complications to be expected with alpha-chymotrypsin (table VI)?

The complications occurring in the alpha-chymotrypsin series are those en-

TABLE V

PERCENTAGE OF EXTRACAPSULAR EXTRACTIONS FOLLOWING USE OF ALPHA-CHYMOTRYPSIN IN DILUTIONS OF 1:10,000 AND 1:5,000

CONCENTRATION	AGE GROUP	% EXTRACAPSULAR
1:10,000	0-49	11
	50+	7
1:5,000	0-49	11
	50+	5

TABLE VI

OPERATIVE COMPLICATIONS
(IDEAL CASES ONLY)

COMPLICATION	PERCENTAGES		
	AGE GROUP		OWENS & HUGHES
	0-49	50+	
Vitreous loss	4	3	9
Vitreous presentation without loss	1	3	8
Hemorrhage	2	1	no data
Posterior dislocation of lens	0	0.2	no data

countered during any cataract surgery. Vitreous loss is still a factor to be reckoned with. The incidence in this series is relatively small compared to the incidence in the Owens and Hughes series. This may be due to other advances in cataract surgery made during the past fifteen years. Improved akinesia and methods to soften the eye and reduce orbital pressure have contributed to the reduction of loss of vitreous.

Hemorrhage, in the cases in which alpha-chymotrypsin has been used, seems to occur more frequently in the younger age group.

Posterior luxation of the lens, on the other hand, appears only in the older age group, that is in 9 cases, or 0.2 per cent of the *total* series.

What are the major postoperative complications (table VII)?

The complications are those encountered after any cataract surgery. The postoperative complications evaluated were those immediate complications which occurred in the first twenty-one days. A future survey should be undertaken to determine the incidence of delayed postoperative complications and their relationship to the use of alpha-chymotrypsin.

TABLE VII

IMMEDIATE POSTOPERATIVE COMPLICATIONS
(IDEAL CASES ONLY)

COMPLICATION	PERCENTAGES		
	AGE GROUP		OWENS & HUGHES
	0-49	50+	
Absent or shallow Anterior Chamber	7	3	no data
Wound reopening	2	2	1
Iris prolapse	0	2	2

You will note that the figures show a greater incidence of absent or shallow anterior chamber in the younger age group.

Wound reopening occurred in higher percentages than that reported by Owens and Hughes, but there was no age factor involved.

Prolapse of the iris showed the same incidence as reported by Owens and Hughes (table VIII).

1. Type of enzyme
2. Concentration
3. Amount
4. Time in solution before use
5. Time in anterior chamber

No outstanding relationship was found using a comparison level of two times and rejecting small numbers of cases.

More case reports are needed before the influence of type of enzyme, its concentration, amount and time in the eye on postoperative complications are definitely ruled out. The comparison level of two times eliminated some figures which might have achieved significance had there been greater numbers of cases.

TABLE VIII

IMMEDIATE POSTOPERATIVE COMPLICATIONS (CONT.)
(IDEAL CASES ONLY)

COMPLICATION	PERCENTAGES		
	AGE GROUP		OWENS & HUGHES
	0-49	50+	
Hyphema	6	4	5
Uveitis	7	6	7
Corneal Edema or Striate Keratitis	21	14	no data
Endophthalmitis	0	0.5	0.5

The incidence of hyphema, uveitis and endophthalmitis is no different from that reported in the other series.

Corneal edema and striate keratitis occur in approximately one of five eyes in the younger age group and one of seven eyes in the older age group. This is definitely a high incidence.

Is there any relation between the development of uveitis, hyphema, wound reopening, iris prolapse, corneal edema and striate keratitis (in ideal cases) to the following factors?

The data just presented suggest that our operative results might be improved if certain points of technique are emphasized and others are modified.

1. A 1:10,000 dilution is as effective as a 1:5,000 dilution, according to our data. Therefore it would seem that the higher dilution would be advisable, since side effects may be less.

It also appears advisable to use a freshly prepared solution (within one-half hour of dilution).

2. In order to attain maximum effective zonulolysis and lessen the danger of damage to the endothelium, irrigation with alpha-chymotrypsin should be done with a blunted cannula underneath the iris. No more than 2 cc. of enzyme solution should be irrigated beneath the iris unless inadequate zonulolysis is obtained. In this event additional solution may be used but with added risk.

3. Removal of residual enzyme by irrigation should be confined to the anterior chamber. The posterior chamber should not be irrigated because of increased danger of loss of vitreous. Our studies suggest that the enzyme should not remain in the anterior chamber for more than two minutes after its introduction has been completed.

4. Removal of the lens should be accomplished by a method which avoids contact of the endothelium with the extracting instrument. The data indicate no difference in the numbers of intracapsular extractions obtained with the capsule forceps and with the erisophake.

5. Our data show that the use of fewer than three sutures for closure of the wound resulted in a higher incidence of wound reopening.

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A DOUBLE-BLIND THERAPEUTIC TRIAL OF THE EFFECT OF ALPHA-CHYMOTRYPSIN ON THE FACILITY OF CATARACT EXTRACTION

BERNARD SCHWARTZ, M.D., PH.D.

and

MARTIN CORWIN, M.D.
BY INVITATION

ROBERT ISRAEL, M.S.
BY INVITATION

BROOKLYN, NEW YORK

FOLLOWING the observation of Barraquer (1958)[1,2] that alpha-chymotrypsin facilitates cataract extraction, conflicting results were reported by others. Some investigators felt that there was no increase of facility of cataract extraction, while others believed that alpha-chymotrypsin exhibited a definite effect.[7] Such conflicting data are common in medicine with the introduction of any new drug or surgical therapy based on subjective evaluation.

It was decided, therefore, that a therapeutic trial was required to evaluate the role of alpha-chymotrypsin in facilitating cataract extraction. This therapeutic trial not only would serve to provide objective evidence regarding the effectiveness of this substance, but would also serve as a basis for evaluating operative and postoperative complications. The objectivity of the therapeutic trial would be increased by using the double-blind technique for evaluation.

It is the purpose of this paper, therefore, to report the results obtained with a double-blind therapeutic trial on the facility of cataract extraction with the use of alpha-chymotrypsin. The data will be reported both subjectively, in terms of the individual surgeon's opinion, and objectively, the criterion being the length of time required to remove the lens. The data regarding the operative and postoperative complications will be reported in a subsequent paper.

METHODS

The patients selected for this study were those admitted for cataract extraction at Kings County Hospital, Brooklyn, New York. The age range and sex distribution as well as the cataract type are shown in table I.

The surgeons operating on these patients were third-year residents who already had experienced six months of cataract extractions, numbering about forty or fifty cataract procedures each. In attendance with the resident surgeons was an experienced staff surgeon whose

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Supported by a research grant from the National Society for Prevention of Blindness.

Presented at the Sixty-Fourth Annual Session of the American Academy of Ophthalmology and Otolaryngology, Oct. 11-16, 1959, Chicago.

TABLE I

SOME CHARACTERISTICS OF POPULATION USED IN DOUBLE-BLIND THERAPEUTIC TRIAL OF ALPHA-CHYMOTRYPSIN ON THE FACILITY OF CATARACT EXTRACTION

AGE	NO.	SEX	NO.	CATARACT TYPE	NO.
40-49	4	Male	28	Senile Immature	3
50-59	7	Female	40	Senile Mature	60
60-69	22			Traumatic Mature	2
70-79	21			Hypermature	2
80-89	11			Diabetic	1
90 & over	3				

opinion contributed to the decision of ease of cataract extraction.

The preparation of alpha-chymotrypsin (ophthalmic Quimotrase) used for this study was that prepared by P.E.V.Y.A. Laboratories, Barcelona, Spain. The alpha-chymotrypsin is packaged as a lyophilized sterile preparation, 1 mg. in a vial together with a 5 cc. ampule of 0.9 per cent saline solution as diluent.

In order to obtain a rigid objective evaluation, a placebo was prepared. The placebo consisted only of the diluent, that is, the normal saline solution, and was supplied in a package prepared especially for us by P.E.V.Y.A. Laboratories. This package was exactly the same as the regular Quimotrase preparation containing an ampule of saline solution and a vial for the alpha-chymotrypsin. However, the alpha-chymotrypsin vial was empty. Prior to the surgical operation, the alpha-chymotrypsin vial was taped right up to the stopper so that no view of the contents of the vial could be obtained. Thus neither the nurses nor the surgeons had any knowledge of whether the vial contained alpha-chymotrypsin or was empty.

The nurse was instructed to break open the ampule of saline solution, inject the contents into the alpha-chymotrypsin vial, mix, and then withdraw the solution. Special caution was exercised so that no air space was left in the syringe on withdrawal. This minimized the frothing, since the alpha-chymotrypsin solution had a tendency to froth slightly more than the saline solution. In this way a syringe full of liquid was handed to the surgeon and his assistant, and neither they nor the nurse knew its contents.

The package of alpha-chymotrypsin vial plus saline ampule was marked with a number and the patient's name before the operation, and only one investigator (M.C.) knew which packages contained alpha-chymotrypsin. The same investigator was the only one with a knowledge of the code, and he was in no way connected with the surgical procedure. No indication of which substance the patient received will be placed on the chart until the entire study is completed, that is, until a planned follow-up time of approximately a year and a half has passed. Therefore, neither the surgeon, the assistant, the nurse, the patient, nor

any other ophthalmologist examining the patient during this time interval will have any knowledge as to whether this patient received alpha-chymotrypsin or only saline solution.

The patients included in this study were selected and paired randomly; that is, for each surgeon a chart was constructed containing a random-paired selection of patients, one of the patients of the pair to receive the alpha-chymotrypsin, the other the control saline solution. The random arrangement was taken from standard tables.[3] Therefore, the experience of the surgeon is not of paramount importance, since he will be making a relative judgment of the facility of cataract extraction on patients paired closely in time.

The data obtained were recorded by means of a code sheet. This code sheet was constructed for national distribution by the Committee on the Use of Alpha-chymotrypsin of the American Academy of Ophthalmology and Otolaryngology. Several columns were added to record a rather extensive postoperative follow-up period of eighteen months. Also on the code sheet was an extra column in which the surgical assistant was required to record the length of time necessary to perform the cataract extraction; that is, from the moment when the extracting instrument was applied to the moment when the lens passed through the wound. It was felt that this data would give an additional indication of the possible effect of alpha-chymotrypsin as a zonulolytic agent. If the zonules were weakened by this substance, the time for removal of the cataract would be considerably less than if they were not. The surgeon was asked to evaluate the facility of this cataract extraction in relation to his previous experience; as on the standard code sheet, he was to record either that the cataract extraction was easier or that it was not easier. If the surgeon felt that there was no difference between this cataract extraction and previous cataract extractions, he was requested to answer "not easier."

The data were analyzed by two techniques. The data regarding the facility of cataract extraction were analyzed by the technique of sequential analysis. The method of sequential analysis allows the evaluation of the data as they are obtained. By means of a graph one can determine exactly when enough data have been accumulated to reach a significant level. Then the clinical trial can be terminated. This technique was originated by Wald[8] and is now beginning to be applied to clinical therapeutic trials. Its advantages are its efficiency in assessing the effectiveness of a particular therapy by using the minimum amount of patients in the shortest period of time. Examples of the application of sequential analysis in therapeutic research have been recently published by Doering and Hagans and their colleagues.[4,5] Our colleague, Robert Israel, was of prime assistance to this study in setting up our data to be analyzed by the sequential analytical technique; his methods are outlined in further detail in the appendix.

The data regarding the time taken to remove the cataract were evaluated by the Students "t" test. The mid-point of each time interval group was taken as the mean for that particular group, and the means of the total time intervals were compared statistically, using a p value of 0.05 as the level of significance.

RESULTS

Table II classifies the possible responses obtained for each surgeon on the facility of cataract extraction with the alpha-chymotrypsin solution and with the saline solution control.

TABLE II

SUBJECTIVE RESPONSES OF INDIVIDUAL SURGEONS ON FACILITY OF CATARACT EXTRACTIONS

DRUG	CONTROL	SURGEON			TOTAL
ALPHA-CHYMOTRYPSIN	NORMAL SALINE SOLUTION	X	Y	Z	
+	—	4	6	5	15
—	+	0	0	1	1
+	+	0	3	0	3
—	—	3	2	4	9

+ = Facility of cataract extraction easier.

— = Facility of cataract extraction not easier.

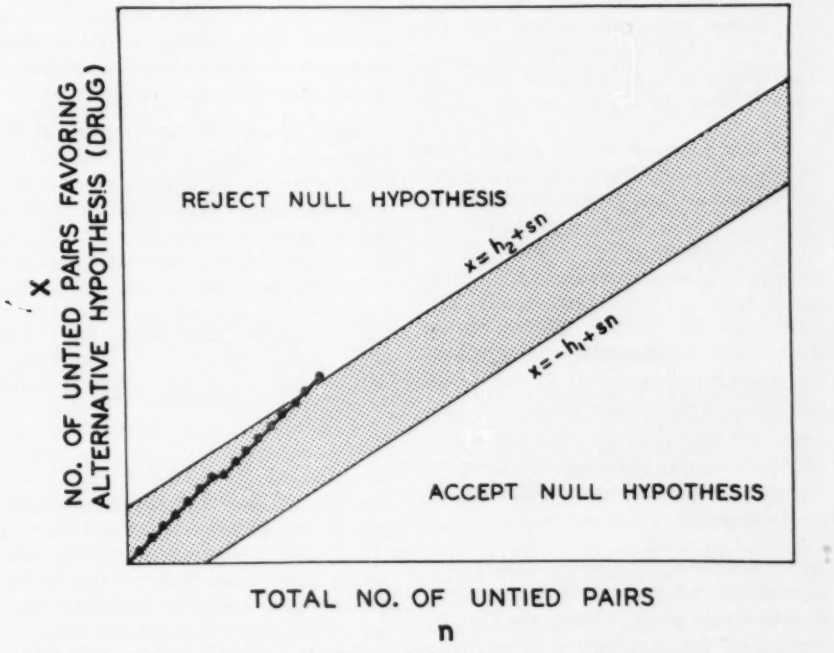

FIG. 1—Sequential analysis graph of effect of alpha-chymotrypsin on facility of cataract extraction.

Only the untied pairs are plotted in the sequential analysis graph (fig. 1). Along the ordinate of the graph is plotted the total number of untied pairs favoring the alternative hypothesis, that is, favoring the action of alpha-chymo-

trypsin. An untied pair favoring the drug indicates that in the treatment of a pair of patients, the surgeon reported an increased facility of cataract extraction in the patient who had received the drug (favorable response), while his report on the other patient of the pair, who had received saline solution only, was that the facility of cataract extraction was not easier (unfavorable response). Thus, there was a positive response (+) corresponding to use of the drug and a negative response (—) for the control. This is an untied pair, since the results are dissimilar in quality for the drug and for the control. A pair is also *untied* if the surgeon reports that the cataract extraction was not easier, when the patient had received the drug, and that it was easier, when the patient was the control and had not received the drug. The total number of untied pairs are plotted along the abscissa of the graph.

As will be noted on the graph, there are two diagonal lines, the area above the uppermost line represents the basis of accepting the therapeutic success of alpha-chymotrypsin when the drug facilitates cataract extraction at least three out of four times with untied pairs. The area below the bottom line represents the basis of rejecting the drug as a failure when it only succeeds in one out of two tries with untied pairs. Furthermore, the lines indicate that our choice of accepting or rejecting the drug on the above bases is correct 99 per cent of the time.

As the data are obtained, they are plotted and a line is formed which, as shown in this graph, crosses the line accepting the favorable action of the drug on the facility of cataract extraction. Sixteen untied pairs were required to obtain a significant result, that is, thirty-two patients. However, many more patients were used in the trial, since many pairs turned up in which a favorable response was obtained both with the drug and with the control, or an unfavorable response was obtained both with the drug and with the control, that is, tied pairs. Also, a number of patients were dropped from the study because such events as cancellation of surgery and errors in assigning the patient to the drug or control caused a pair to be incomplete. The total number of patients used before a level of significance was reached was 68.

The number of tied pairs (table II) again serves to emphasize that many times it is difficult on a subjective basis to estimate whether any particular therapy has a favorable or an unfavorable effect. Only when this is placed on an objective basis, using a double-blind technique, is the element of prejudice for or against the therapy removed.

Table III gives data regarding the duration of cataract extraction in patients receiving alpha-chymotrypsin and in those receiving the saline solution control. Also presented in table III are the results of the statistical analysis comparing the means of the two groups. It can be seen that the duration of cataract extraction was significantly less when patients received alpha-chymotrypsin than when they received saline solution alone.

DISCUSSION

In this double-blind therapeutic trial, both the sequential analysis and the data on duration of cataract extraction indicate in an objective manner that alpha-chymotrypsin definitely facilitates cataract extraction. This confirms the subjective clinical experience of a number of individuals and supplies the objective proof that is needed with the introduction of any new therapeutic substance in clinical medicine. This therapeutic trial also answers the question posed by many

TABLE III

DURATION OF CATARACT EXTRACTION FROM THE TIME OF APPLICATION OF EXTRACTION INSTRUMENT TO DELIVERY OF LENS THROUGH WOUND

TIME	CONTROL	DRUG
	NORMAL SALINE SOLUTION NO.	ALPHA-CHYMOTRYPSIN NO.
Spontaneous	0	0
0-30 sec.	0	0
30 sec.-1 min.	0	14
1-2 min.	9	10
2-3 min.	12	9
3-5 min.	10	0
5-7 min.	2	1
7-10 min.	0	0
10-15 min.	1	0
Mean ± Standard deviation (No.) for each cataract extraction (mins.)	3.2 ± 2.1 (34)	1.6 ± 1.1 (34)
	$p < 0.001$	

individuals using the enzyme who have wondered whether this cataract extraction would have been just as easy without the use of alpha-chymotrypsin.

It is interesting to note that there were nine patient pairs (table II) in which the surgeon felt that there was no difference between the facility of cataract extraction with the use of alpha-chymotrypsin and that with the saline solution alone. A search of the data code sheets at the present time fails to indicate any common particular circumstance that would obliterate the facility of cataract extraction with alpha-chymotrypsin. Whether this is due to individual variation in regard to the surgeon's personal experience is difficult to determine. Other factors, such as patient's age and the length of time the enzyme was in solution, may be responsible. The collection of further data is continuing and this problem will again be discussed in a subsequent study together with operative and postoperative complications in the use of alpha-chymotrypsin.

SUMMARY

An evaluation of the effect of alpha-chymotrypsin on the facility of cataract extraction has been conducted by means of a double-blind therapeutic trial. The data regarding the surgeon's subjective experience in the facility of cataract extraction have been analyzed by the method of sequential analysis. The data regarding the time required for removal of the cataract after the application of the extraction instrument have been analyzed by Student's "t" test. Both sets of data support the subjective clinical experience of Barraquer[1,2] that alpha-chymotrypsin significantly facilitates cataract extraction.

APPENDIX

ROBERT ISRAEL, M.S.

Sequential analysis, the statistical technique of testing a hypothesis used in this study, may be described as follows: A rule is given for making one of the following three decisions at any stage of the experiment: (1) accept the hypothesis, (2) reject the hypothesis, (3) continue the experiment by taking another observation.[8] On the basis of the first observation, one of the three decisions is made. If it is the first or second decision, the process terminates. If the third decision is made, a second observation is taken. Then, on the basis of the first two observations, one of the three decisions is made, and so on, until such time that either the first or second decision is reached. Thus, the number of observations (n) required by such a test procedure is a random variable, since the value of n depends on the outcome of the observations. However, statistical theory shows that in repeated tests of the hypothesis in question, the sequential procedure would require fewer observations, on the average, than the comparable fixed sample size procedure. Therefore, in any one experiment, the sequential procedure may or may not require more observations than a similar fixed sample size test; but in the long run, sequential tests will require fewer observations than other tests.

In this study it was desired to determine whether alpha-chymotrypsin facilitates cataract extraction. Observations were made on pairs of patients, both of whom underwent surgery for removal of a cataract, but only one of whom received the enzyme in question; the other received saline solution. A double-blind technique was used by setting up, for each surgeon involved in the study, a random series of assignments of drug and of saline solution in such a way that in each group of four consecutive operations, two patients would receive the enzyme and two would receive saline solution alone.[3] This was done to facilitate the pairing process. In each group of four operations, the first patient receiving the enzyme was paired with the first patient receiving saline solution. In this way, the pairs were made up so that both members of each pair had their operations at approximately the same point in time, and had the same surgeon. The assignment of the enzyme and the pairing process were handled by a doctor not otherwise involved in the study. After the completion of each operation, the surgeon rated the procedure as either "easier than the usual cataract extraction," or "not easier than the usual cataract extraction." If (+) is used to denote the response "easier" and (—) to denote the response "not easier," the results, after pairing, could be tabulated as follows:

		Patients Receiving alpha-chymotrypsin (+)	(—)
Patients Receiving Saline Solution	(+)	w	y
	(—)	x	z

where w, x, y, and z represent the frequency of (++), (+—), (—+) and (——) pairs, respectively. Obviously, the (++) and (——) pairs do not tell us whether the enzyme has any more value than saline solution in the removal of cataracts. They are known as "tied

pairs." The (—+) pairs indicate an unfavorable response to the enzyme, while the (+—) pairs indicate a favorable response. These are known as "untied pairs."

Now, if there is no difference between enzyme and saline, we would expect frequency x and frequency y in the table above to be equal, on the basis of chance alone. Therefore, the null hypothesis H_O which we want to test can be formulated:

$$H_o : \ominus_1 = \frac{x}{x+y} = 50\%$$

An alternative hypothesis H_A, which would be accepted if H_O is rejected, can be chosen:

$$H_A : \ominus_2 = \frac{x}{x+y} = 75\%$$

Furthermore, it was felt that the probability of rejecting H_O when H_O is true should be less than or equal to 1 per cent ($\alpha \leq .01$), and the probability of accepting H_O when H_O is false also should be less than or equal to 1 per cent ($\beta \leq .01$).

With this preliminary information we can formulate the rule necessary for making the three possible decisions in the sequential test:

Let x = the number of untied pairs favorable to the drug [(+—) pairs]
n = the total number of untied pairs [(+—) and (—+) pairs]
u_1 = odds ratio corresponding to $\ominus_1 = 1/1 = 1$
u_2 = odds ratio corresponding to $\ominus_2 = 3/1 = 3$
$\alpha = \beta = 0.1$

Then if $x \leq -h_1 + sn$, take decision (1) (accept H_o)
if $x \geq h_2 + sn$, take decision (2) (reject H_o)
if $-h_1 + sn < x < h_2 + sn$, take decision (3) (take another observation)

where

$$h_1 = \frac{\log \frac{1-\alpha}{\beta}}{\log \frac{u_2}{u_1}} = 4.18$$

$$h_2 = \frac{\log \frac{1-\beta}{\alpha}}{\log \frac{u_2}{u_1}} = 4.18$$

$$s = \frac{\log \frac{1+u_2}{1+u_1}}{\log \frac{u_2}{u_1}} = 0.63$$

By drawing on graph paper the lines $x = -h_1 + sn$ and $x = h_2 + sn$, it can be seen that these two lines divide the graph (fig. 1) into three regions. The region below $x = -h_1 + sn$ is the region of acceptance of the null hypothesis, the region above $x = h_2 + sn$ is the region of rejection of the null hypothesis, while between the two lines lies the region where another observation must be taken. Therefore, if x is plotted against n, as the experiment proceeds we can tell graphically which of the three possible decisions pertains after each pair has been evaluated.

As can be seen in the graph, after a total of sixteen untied pairs ($n = 16$), the upper line was crossed, the decision to reject H_O (accept H_A) was made, and the process terminated. We, therefore, conclude that alpha-chymotrypsin does facilitate the extraction of cataracts; in fact, the proportion of untied pairs that favor the drug may be 75 per cent or more. The probability that this sequential test has led us to the correct decision is equal to or greater than 0.99.

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SUMMARY

DERRICK VAIL, M.D., *Chairman*

WE have heard from Dr. Schwartz that this enzyme isolated by Kunitz and Northrop has been available since 1933. It is a protein and thus is capable of producing an allergic reaction in the eye in sensitized individuals. Clinically, however, this seems to be more of a theoretical than a practical consideration, although such a possibility must be borne in mind and cases of allergic reactions following systemic use have been reported. Alpha-chymotrypsin is a proteolytic enzyme, having a specificity of action at certain peptide bonds, but it is capable of hydrolyzing other bonds such as esters, amides, hydroxyamides, hydrazides, and even carbon-carbon bonds. The optimum pH for maximum velocity of hydrolysis of protein and synthetic substrates by alpha-chymotrypsin is usually between 7 and 9.

Certain enhancers and inhibitors of the enzyme have been discovered. Among the enhancers is calcium chloride, sometimes used in the vehicle for ophthalmic use. It should be borne in mind that while calcium chloride may enhance the effect of the enzyme, it also may prolong its activity. Further investigation of this point must be carried out.

Among the inhibitors are DFP and beta-phenyl-proprionic acid. What, if any, practical use will develop from this information is hard to see at this stage of our knowledge.

Dr. von Sallmann helped us very much when he reported that he was unable to produce an allergic reaction in animals experimentally sensitized to this enzyme by instillation or by injection subconjunctivally, or in the anterior chamber, or in the vitreous. This evidence supports wide clinical impressions.

His studies on the effects of this substance on the corneal endothelium are of great importance to us. His illustrations show these effects beautifully. However,

we are told that the injection of a 0.9 per cent solution of sodium chloride by itself will produce the same type of injury, although to a lesser degree. In other words, the addition of alpha-chymotrypsin is a slight increment in potential damage to the endothelial cells. This is important in considering the question of the cause of striate keratitis, which is found more frequently when alpha-chymotrypsin is used than otherwise.

However, when the enzyme reaches into the corneal stroma through extensively damaged endothelium, a heavy opacity results. Such opacities also occur with a 0.9 per cent solution of sodium chloride. The corneal changes are of a transient nature as a rule, and Dr. von Sallmann concludes that it was improbable that a specific enzymatic action was the cause of the lesion. Using a different technique, which may or may not be a factor, David Shoch and his co-workers found no evidence of endothelial damage in the eyes of twenty-four rabbits. This discrepancy in the findings needs to be resolved.

Finally, Dr. von Sallmann confirms the histologic findings of the St. Louis workers, Ley, Holmberg and Yamashita, who showed by electromicroscopic studies that the zonule fibers are fragmented by the action of the enzyme.

Dr. Maumenee gives us a horrifying picture of what happens when the retina is placed in a solution containing 150 units of alpha-chymotrypsin. However, this concentration and the duration of exposure exceed, by far, the same factors when alpha-chymotrypsin is employed in cataract surgery.

Maumenee's report shows that the supporting structure of the retina is more sensitive to the enzyme than is the rest of the retinal tissue. This damage occurs when alpha-chymotrypsin is injected into the vitreous of an experimental animal. This may have some clinical importance in suggesting that the enzyme should not be used in cases of fluid vitreous or subluxated lens, or where the hyaloid membrane is not intact.

Dr. Troutman's report involved an enormous amount of analytic work on the questionnaires and is still somewhat incomplete. However, enough facts have been gathered to warrant the following conclusions:

1. The incidence of striate keratitis is greater when the enzyme is employed. We believe that this is due largely to mechanical injury to the endothelium by instruments, either forceps or erisophake (about equal incidence). The marked decrease in the depth of the anterior chamber consequent to the forward dislocation of the lens means much less room for manipulation and a greater chance for rubbing or scraping of the endothelium of the cornea than otherwise. The deleterious action of a solution, either of saline solution or alpha-chymotrypsin, upon the corneal endothelium must be considered a part of this problem. The preparation of the solution and the vehicle used may also play a part. As yet we don't know.

2. A 1:10,000 dilution is as effective as a 1:5000 dilution. This finding conflicts with the experience of Barraquer and needs further investigation.

3. Great care must be devoted to the preparation of the fresh solution, the technique and instrumentation of its injection into the posterior chamber, and its removal by irrigation of the anterior chamber two minutes after injection.

4. A very high percentage of surgeons "felt" that the facility of extracting the lens was enhanced by use of the enzyme. This clinical impression was

beautifully supported by the double blind study conducted by Dr. Schwartz.

5. One of the most important findings of this statistical study is the marked decrease in the number of ruptured capsules that occurred when the enzyme was employed in the operation on one eye, when compared with the incidence of ruptured capsules that occurred in the other eye of the same individuals when the enzyme was not used. In other words, the use of the enzyme means fewer ruptured capsules.

6. While we cannot be sure, because of the difficulty in getting figures in a comparable control series, we believe that the complications that occur during the operation or during the healing postoperative stage are no greater or no less whether the enzyme is used or not. The one and major exception to this statement is the finding that 0.2 per cent of the total cases had posterior luxation of the lens, a most serious complication, although known to occur rarely in cases in which the enzyme was not used. The figures Dr. Troutman has given us regarding the presentation of vitreous and the actual loss of vitreous seem high, and they probably are, but we do not know what the percentages would be in an up-to-date comparable control series. Theoretically, at any rate, we should expect a higher percentage of loss of vitreous when the enzyme is used, considering that we are dealing with a dislocated lens.

7. Is the incidence of absent or shallow chambers greater when the enzyme is used? This was a difficult question to answer. Much depends on the technique of the operation, i.e., type of incision, whether multiple sutures were used, and so on. Our figures do show an increase of such cases, especially in the lower age group. Reports in the literature on the use of alpha-chymotrypsin indicate that wound healing is not retarded, and catgut sutures do not dissolve. More facts are needed.

8. Barraquer and others have mentioned the occasional case in which edema of the conjunctival flap has occurred. Our studies give us no information on this point. Barraquer believes that this is due to (a) incision too far in the cornea and (b) lack of proper wound closure.

9. It is possible that the round pupil operation has fewer complications than result from complete iridectomy. More study along this line is needed.

10. This report cannot tell us anything of the late effects of the use of alpha-chymotrypsin; the time is too short. A further report on this series a year or so from now should be made. We know from Dr. Maumenee's experimental studies that the retina can be damaged by the enzyme when it is injected into the vitreous. We don't know whether the pars ciliaris retinae is injured under the conditions of cataract surgery by seepage of the enzyme into Petit's canal. If it is, a higher incidence of aphakic retinal detachment might be expected. If it isn't, a lower incidence might occur, because the mechanical pull of the zonular fibers is abolished during the operation.

11. Modifications of our present technique and new instrumentation devised to assist us in the removal of the lens in view of the altered conditions because of zonulolysis will undoubtedly occur.

On the basis of the information obtained from this and a partial survey of the growing literature, your Committee recommends that alpha-chymotrypsin should not be used in the surgery of the lens in the following conditions:

1. Cases in which the patient is under twenty years of age
2. Cases of endothelial dystrophy
3. Cases of subluxated lenses
4. Cases of traumatic cataract, especially when vitreous is presented.

Finally, we beg you to remain conservative in your actions regarding the use of zonulolysis until we know much more about it.

Your Committee regrets that there remain a large number of questions that it is unable now to answer. Further long-term studies will be made either individually or by the Committee as a whole, and the results reported.

All of us wish to thank the members of this Academy who have supplied us the answers to the questionnaire that was sent out. It was tedious work, honestly performed, and we collected much information of great value. We are impressed with the exceedingly high quality of cataract surgery being done throughout the country.

As Chairman of the Committee, I wish to compliment the members of the Committee for their loyal cooperation and hard work, and to thank them publicly for their enthusiasm and support.

ALPHA-CHYMOTRYPSIN IRRIGATING CANNULA

KENNETH L. ROPER, M.D.
CHICAGO, ILLINOIS

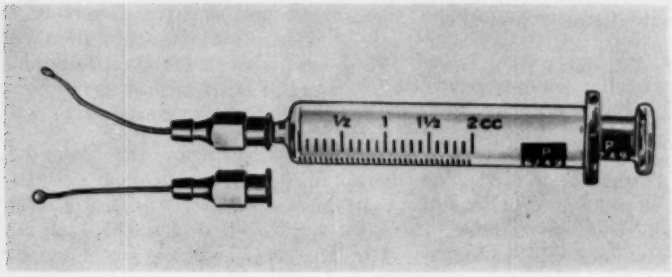

FIGURE 1.

THE tips of most anterior chamber irrigators are designed for introduction between the lips of the wound and are unsuitable for the instillation of the enzyme alpha-chymotrypsin under the iris.

An irrigating cannula extending from a Luer hub with a curve near the end conforming to the anterior lens surface, and a flattened, round, symmetrical tip has been designed for this new procedure (fig. 1).* Two openings are provided in the tip—at the equator on each side rather than at the equator below (fig. 2).

The cannula, attached to a 2 cc. syringe, is introduced through the section and carefully passed beneath the pupillary edge of the iris at 6 o'clock.

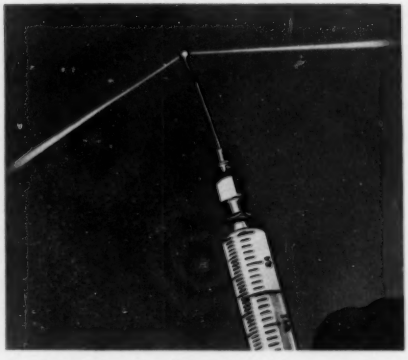

FIGURE 2.

The tip should not be advanced so far that the hyaloid membrane will be ruptured or the vitreous dislodged, but it must be inserted far enough so that the enzymatic solution will be sprayed across the fibers of the zonular ligament attached to the anterior capsule. The tip can then be moved to the 2 o'clock position and to the 10 o'clock position, in each instance spraying about 0.5 to 0.75 cc. of the solution (fig. 3). The tip is

Presented as a *New Instrument* at the Sixty-Fourth Annual Session of the American Academy of Ophthalmology and Otolaryngology, Oct. 11-16, 1959, Chicago.

*Made by V. Mueller & Co., Chicago.

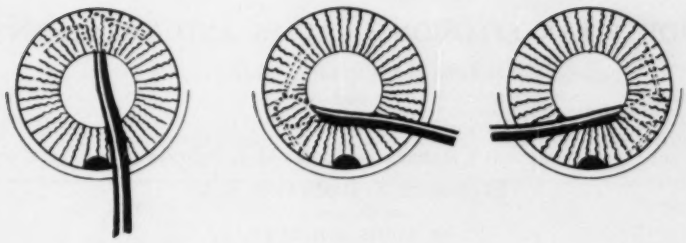

FIGURE 3.

then attached to an anterior chamber irrigating bulb for the copious irrigation of the anterior and posterior chamber after the elapse of sufficient time for zonulytic action.

The flattened, round, symmetrical tip, similar to the tip of Callahan's zonule stripper,[1] eliminates an accidental tear of the anterior lens capsule or of the iris itself. The two openings at the sides of the flattened tip give a gentle diffusion of the solution both clockwise and counterclockwise from the 2, 6 and 10 o'clock positions. Adequate irrigation of the superior zonules is obtained without having to introduce the tip through a peripheral iridotomy or iridectomy opening as many surgeons are now doing.

A stream coming straight out of the tip of a cannula might not only be too forceful but also track far beyond the intended target. This fact seems to be of considerable importance in the light of a committee report on the use of alpha-chymotrypsin in ophthalmology, made at the 1959 Annual Meeting of the American Academy of Ophthalmology and Otolaryngology.[2] Accumulated data reveal that serious damage to the retina can occur when injections are made into the vitreous. The committee therefore suggested that the enzyme not be used in cases of fluid vitreous, or subluxated lenses, or where the hyaloid is not intact—as in most traumatic cases. It behooves the surgeon to employ a method of injecting alpha-chymotrypsin into the posterior chamber that will not penetrate the vitreous body.

The above committee further recommended that alpha-chymotrypsin not be used in patients under 20 years of age, and in cases of endothelial dystrophy. Finally, the committee entered a plea for conservatism regarding the use of zonulolysis until much more is known about it.

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MIDDLE EAR EFFUSIONS: CAUSES AND TREATMENT

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THE increasing incidence of middle ear effusions has provided the clinician and the investigator with a challenging problem, yet we have made little progress in the understanding of etiology and pathogenesis. Some of the prevalent etiologic concepts appearing in the literature are not supported by unequivocal experimental or clinical evidence. As a consequence, therapy of this group of diseases based on these concepts is uncertain and often contradictory.

One of the most perplexing problems encountered in dealing with middle ear effusions is the variety of terms used to describe the types of effusions which may be associated with diseases of the middle ear and the eustachian tube. A review of the literature, which illustrates the confused state regarding terminology and the divergent opinions and findings, has been presented previously.[31]

In order to obtain clarification and agreement in terminology, there must be some acceptable criteria by which the categories of effusions can be defined and differentiated. Many investigators have attempted to distinguish between the types on the basis of otologic findings and physical characteristics of the fluid, while a few have used chemical properties as a basis for their classification.

In recent years, much attention has been given to the nature of the cells found in middle ear effusions. Our own investigations have led us to agree that, at present, a microscopic examination provides the best data available for grouping effusions into meaningful categories. Such a classification was worked out and is shown, together with contemporary clinical terminology, in table I. Details of the methods of investigation and the clinical, cytologic, bacteriologic and chemical data in human patients were previously presented.[31]

As a means of investigating further the mechanism through which effusions occur in the human middle ear, an attempt was made to produce similar disease in dogs by electrical cauterization of the nasopharyngeal orifice and the immediate peritubal area of the eustachian tube.[30] All middle ears were aspirated at planned intervals after cautery, and the effusions were collected for studies similar to those which were performed on human specimens.[13,30]

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TABLE I

CLASSIFICATION AND CHARACTERIZATION OF MIDDLE EAR EFFUSIONS

DIAGNOSIS OF THE EFFUSION	CLINICAL SYNONYMS FOR THE DISEASE	MICROSCOPIC CHARACTERISTICS		
		CELLULAR REMNANTS	NEUTROPHILES	MUCOUS STRANDS
Serous	Otitis Media with Effusion Secretory Otitis Secretory Catarrh	Rare	Rare	None
Purulent	Suppurative Otitis Media Acute Otitis Media	Moderate	Numerous	Rare
Mucopurulent	Chronic Otitis Media Glue Ear Catarrhal Otitis Media Mucoid Ear Allergic Ear (?) Secretory Otitis Media	Numerous	Few	Numerous
Mucoid	Same as for Mucopurulent	Rare	None	Myriads

DISCUSSION OF FINDINGS

This report of findings in humans is based on the examination of 223 specimens of middle ear effusions obtained from 159 patients. These data include those on 157 specimens from 105 patients which were reported previously.[31] As shown in table II, 202 specimens have been examined cytologically, 181 by bacterial culture, and 34 by chemical analyses. The data for experimentally produced effusions in animals, which were obtained on 24 specimens taken from six dogs, are summarized later.

TABLE II

NUMBERS OF PATIENTS AND SPECIMENS EXAMINED

Patients with Middle Ear Effusions	159
Total Specimens of Effusions	223
Specimens Examined Cytologically	202
Specimens Examined Culturally	181
Specimens Examined Chemically	34

Cytologic examination of the human effusions, which was the basis for our classification (table I), revealed the following:

Serous effusions contained essentially no cells nor cellular material, although an occasional neutrophile, lymphocyte, large phagocyte or cellular remnant was found. These effusions were pale straw to salmon in color, low in viscosity, and easily removed from the ear.

Purulent effusions were those which, on microscopic examination, showed myriads of intact neutrophiles and a moderate number of mucous strands and cellular remnants as their predominant characteristics. Occasionally, large and small phagocytes and a few lymphocytes were found. These effusions, which were grey-white, turbid, fairly homogeneous, and slightly increased in viscosity, were characteristic of the classical cases of suppurative otitis media. There was some tendency for

the cellular constituents to settle out, so that a biphasic appearance developed in the fluid upon standing.

The *mucopurulent* specimens contained numerous mucous strands and large numbers of cells, mostly of the mononuclear type, in various stages of degeneration. Some neutrophilic nuclear remnants and a few intact neutrophiles were also found. These specimens were highly viscid and sticky, usually fairly translucent and homogeneous, varying in color from yellow to rather dirty grey. These were difficult to aspirate from the middle ear and awkward to handle during analyses because of their tenacious, viscous physical properties.

A *mucoid* category of effusions was also established. These differed from the mucopurulent effusions in that they contained very few, if any, cellular remnants. Like the mucopurulent effusions, they contained myriads of mucous strands. Neutrophiles, lymphocytes and phagocytes were rare or absent.

Much emphasis has been given to an allergic etiology for middle ear effusions. We believe that the mucopurulent and mucoid categories encompass the type which most authors refer to as the "allergic ear" in the human. Jordan,[22] Koch,[24] and Ivstam[21] reported a high incidence of eosinophiles in aural or nasal secretions, or have pointed out the high correlation between a state of hypersensitivity and the presence of middle ear effusions. Proetz,[28] Dohlman,[7,8] Shambaugh,[32] and Derlacki[6] have written about the importance of an allergic evaluation in patients with nonresponsive otitis media.

With reports of an allergic category in mind, careful attention was paid to the number of eosinophiles present in the aspirated effusions. Despite a thorough cytologic study using Wright and Papanicolaou stains, only 11 of the smears showed a single eosinophile in the entire slide. One specimen showed five eosinophiles per high power field and another showed three. A superficial review of nasal findings, eosinophiles in the peripheral blood and response to antihistaminic therapy failed to indicate that allergy was an important etiologic factor in our series of cases.

The distribution of 202 human specimens into our four categories of effusions is shown in figure 1. The mucopurulent specimens were most prevalent among those patients upon whom myringotomy was performed, constituting 51 per cent. The serous comprised 25 per cent, purulent 18 per cent, and the mucoid only 6 per cent of the specimens examined.

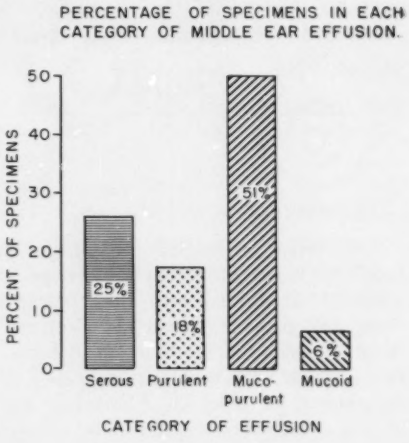

FIGURE 1.

The incidence of these types of effusions with regard to age of the patients is shown in figure 2. The greatest number of mucopurulent and purulent specimens fell into the groups below 8 years of age, while the serous specimens were obtained over a wide age range, with

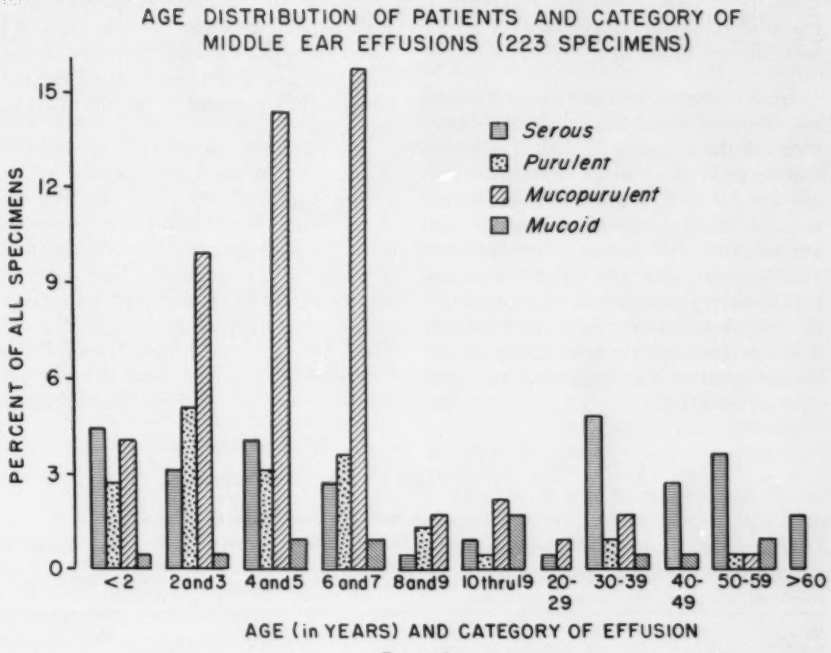

FIGURE 2.

some predominance in the groups below 8 and over 30 years. The mucoid group appeared to be distributed evenly throughout, except for a slight increase in the age bracket from 10 to 19 years.

On the basis of the cytologic picture, twenty of the 24 specimens collected from dogs were classified as purulent, three were serous, and one was mucopurulent.[30] Most of the animal effusions showed a predominance of polymorphonuclear cells and a relatively small number of lymphocytes and monocytes. During the 26 days of the experiment, there was no decrease in the number of polymorphonuclears nor any increase in the percentage of lymphocytes, monocytes or macrophages. Only a small number of cellular remnants were seen in these effusions and never occurred to the degree seen in human material. Eosinophiles were not present in increased numbers at any stage of the observations.

Differences in physical and cytologic characteristics of the experimental effusions were not found to correlate with the length of time that the effusion was present in the middle ear.

There is general agreement that purulent otitis media is most frequently secondary to bacterial infections,[9,11,15,20,25] but many investigators were unable to culture bacteria from middle ear effusions, or considered that the growth obtained was from contaminants.[4,16-18,23,29,36,38] Siirala and others reported positive cultures in a small percentage of their

cases.[10,22,33] An occasional reference is made to the presence of bacteria on direct smears of middle ear effusions.[2,19]

Direct smears of the effusions which we obtained from humans were examined for the presence of inclusion bodies and bacteria. Specimens were also studied by culturing them aerobically and anaerobically for bacterial growth. Examination of the smears revealed certain bacteria, but no typical inclusion bodies were found which might have indicated viral activity. The bacteriologic findings for culture and smear of the human effusion specimens are summarized in table III.

Just as in the findings in humans, a high percentage of the middle ear specimens from dogs showed bacteria on culture and smear (91 per cent of the cultures and 71 per cent of the smears positive).

In order to check the validity of the rather high percentage of positive cultures which we obtained, as compared with the findings of other investigators, a group of 24 specimens was collected with special efforts to avoid contamination during their removal from the ear, after the canal had been cleaned and "sterilized." Positive cultures were obtained from 12 of these 24 specimens and bacteria were present on smear in three of them.

TABLE III

BACTERIAL CULTURES AND SMEARS OF MIDDLE EAR EFFUSIONS

CATEGORY	NUMBER OF SPECIMENS	POSITIVE CULTURES OBTAINED	SMEARS CONTAINING BACTERIA
Serous	51	18	4
Purulent	37	14	3
Mucopurulent	93	37	29
Total	181	69	36

Approximately 35 per cent of the serous specimens gave positive cultures, showing primarily micrococci and an occasional streptococcus. A few of the smears (8 per cent) revealed a small number of cocci and bacilli. Also, on culture, about 38 per cent of the purulent specimens were positive for the same group of organisms, while 8 per cent of these smears showed cocci. Positive bacterial cultures were obtained in 40 per cent of the mucopurulent specimens, and in addition to the above species, pneumococci, Friedlander's bacilli and Proteus were recovered. Thirty-one per cent of these effusions revealed microorganisms on smear.

Thus the findings in this selected group substantially supported the findings in the larger group, especially regarding the high incidence of positive cultures obtained. A review of the genera of bacteria in the special series revealed a distribution similar to that in the larger group.

There has been considerable diversity of opinion regarding the significance of positive bacterial cultures obtained from the effusions. Our efforts to clean and sterilize the ear canal with alcohol in the selected group of cases failed to reduce

the incidence or distribution of these organisms. In our data, it is possible that a large proportion, if not all, of the micrococci cultured might have been contaminants picked up in the meatus, since these organisms are part of the endogenous flora of the ear canal.

On the other hand, one does not usually find streptococci, pneumococci or Friedlander's bacilli in the normal meatus. Furthermore, the high percentage of specimens in which bacteria were found on direct smears is of importance. These bacteria must have been present prior to myringotomy, since there was not enough time for a contaminant to have multiplied sufficiently to account for the numbers of bacteria found on most of the slides.

It is assumed that cautery of the tubal lumen and peritubal area in dogs resulted in a nasopharyngitis. A salpingitis and otitis media apparently followed as a consequence of the extension of the infection from the nasopharynx into the middle ear. As a result of the smoldering bacterial infection in the tympanum there was a continuous accumulation of fluid in the middle ear lumen and a persistent migration of neutrophiles into the effusion.

Previous investigators have been interested in various aspects of the chemical properties of effusions. Several have measured the protein content, attempting thereby to distinguish between exudates and transudates, while others have measured different components to aid in characterizing various types of effusions. A few have suggested that the gross physical properties of the fluids are dependent primarily upon the total dry-matter content. Our review of the literature[31] indicated that there is some disagreement with regard to chemical findings and their interpretation.

In our own studies of effusions obtained from both humans and dogs, we have measured total protein, total dry matter, deoxyribonucleic acid (DNA), and carbohydrate bound to protein (figs. 3 and 4). DNA is that component of nucleoproteins which is found primarily in cell nuclei, and the carbohydrate bound to protein is presumed (but not actually proved) to be a mucopolysaccharide. The analyses were performed in order to gain more information about the nature of the differences between various types of middle ear effusions. Specimens of blood serum were also subjected to the same analyses in order to compare the compositions of middle ear effusions with those of sera, and to determine the possible relationships between them.

The results of the biochemical determinations are summarized graphically in figures 3 and 4. Data on human mucoid effusions are not included because there were not enough of these specimens for representative analyses. The data on experimentally produced effusions in dogs include only serous and purulent types, since there was only one mucopurulent and no mucoid specimens obtained. The human blood sera were obtained from normal subjects, whereas the dog blood sera were obtained from both experimental and control dogs.

In human middle ear effusions we found that the serous and mucopurulent specimens, which differed greatly in physical properties, contained nearly the same percentages of dry matter. These findings indicate that the viscosity of the effusions does not depend primarily upon the total content of dry matter. All effusions, in both humans and dogs, had higher average dry matter content than the respective sera.

The total protein and the other organic constituents were reported as per-

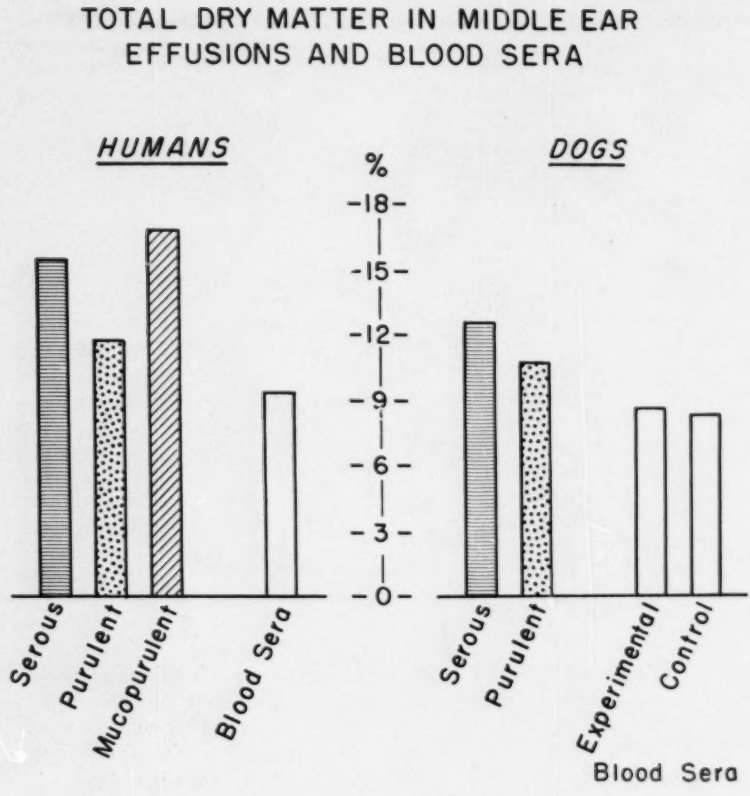

FIGURE 3.

centages of the dry matter. The protein content of human purulent and mucopurulent specimens was nearly the same as that of the sera, but that of serous effusions was a little higher (fig. 4). Likewise, in dog specimens the serous were somewhat higher and the purulent a little lower in protein content than the blood sera.

Of those constituents which were measured, the deoxyribonucleic acid showed the greatest differences between the categories. The purulent effusions were relatively high in DNA content, the mucopurulent were intermediate, and the serous were quite low. Sera contained only traces of DNA. Since DNA is found in high concentration in cell nuclei, it was not unexpected that purulent specimens, which contained large numbers of polymorphonuclear leukocytes, had the highest DNA content. The mucopurulent specimens, which usually had only a few polymorphonuclears, but many cellular remnants, contained sizeable amounts of DNA, but not as much as the purulent effusions.

COMPONENTS IN MIDDLE EAR EFFUSIONS AND BLOOD SERA
(As Percentages Of Dry Matter)

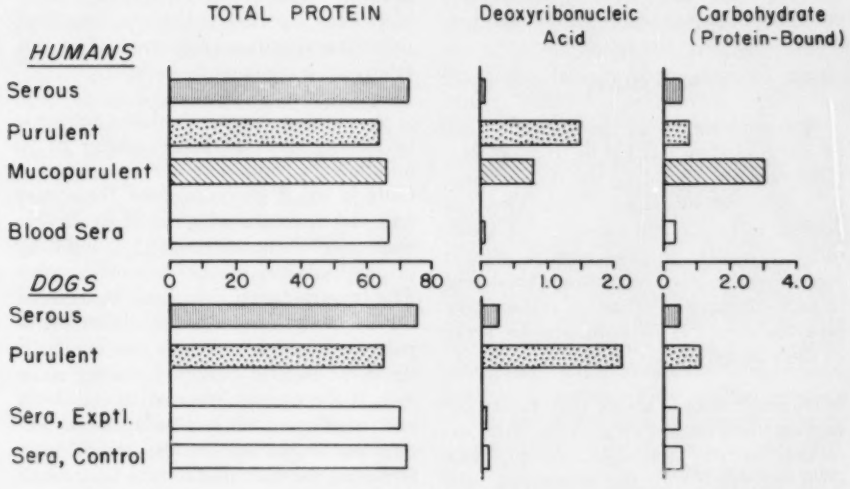

FIGURE 4.

A few of the purulent specimens from dogs were subjected to ultracentrifugation, and when the cells and cellular debris were thus removed, the supernatant solutions contained approximately the same concentration of DNA (and also protein-bound carbohydrate) as the serous specimens. This finding indicated that the presence of cells and cellular material appeared to be chiefly responsible for the chemical differences between the serous and purulent categories.

The carbohydrate bound to the protein was present in much higher concentration in the mucopurulent effusions than in any others. The purulent specimens contained a slightly higher percentage of protein-bound carbohydrate than serous effusions and blood sera, but not nearly as high as the mucopurulent. These findings were interpreted to indicate that mucopurulent specimens were particularly rich in "glycoproteins," in amounts far in excess of those found in serous or purulent specimens. The source of this mucopolysaccharide or glycoprotein is still a matter of speculation, but it is not present in blood serum in sufficient concentration to provide the amounts found in mucopurulent effusions. The mucous strands which were observed in cytologic examination undoubtedly contributed to the high content of protein-bound carbohydrate.

In general, the percentages of the components in the experimentally produced middle ear effusions in dogs were not very different from those in the corresponding categories (serous and purulent) of human specimens. Likewise, the human and animal sera did not seem to differ much in the components measured.

Paper electrophoreses of the supernatants of ultracentrifuged effusions and sera from dogs indicated that there were no consistent differences by which they could be distinguished from one another.

TREATMENT

A consideration of the literature and of our own data has led us to adopt certain concepts regarding the development of middle ear effusions. These ideas, of course, influence the rationale of treatment. It is our purpose now to present recommendations regarding treatment in each category of effusion, and to show how the concepts of pathogenesis serve as their bases.

During an acute upper respiratory infection there occurs viral or bacterial infection of the nose and nasopharynx with extension into the eustachian tube and middle ear. An inflammatory reaction, including dilatation of blood vessels and lymphatics, develops and there follows an extravasation of cellular and noncellular constituents of the blood into the epithelium of the tube and the mucoperiosteal lining of the middle ear. A variable amount of fluid and an occasional cell extravasate through the intact mucoperiosteum into the lumen of the tympanum, producing the *serous* type of effusion.

If adequate immunity is present (as in most adults), the invading microorganisms are inactivated or destroyed. After the upper respiratory infection is controlled, the effusion is either resorbed by the lymphatics or blood vessels, or swept down the eustachian tube into the nasopharynx. Frequently, it is expedient to mobilize the thin serous fluid by continuous pressure politzerization of the eustachian tube and the middle ear. If this procedure is unsuccessful, puncture myringotomy followed by inflation can be performed as an office procedure. Since we desire prompt and rapid thinning of the intact mucoperiosteum and wish to avoid secondary infection, we usually prescribe broad-coverage antibiotics for a period of three to four days following myringotomy, even after this relatively innocuous procedure.

We cannot comprehend the rationale of placing an indwelling catheter in all middle ears containing serous effusions. Only a small percentage of these ears will fail to clear under medical management and evacuation of the fluid by proper inflation of the eustachian tube. The manipulation involved in routine myringotomy and the insertion of a polyethylene tube, even in the hands of the most skillful otologist, causes some loss of the fibrous layer of the eardrum and results in the implantation of exogenous organisms in the middle ear. Granting the fact that only a very small percentage of these ears will become infected, we believe that the performance of myringotomy and the insertion of indwelling catheters in serous otitis media should be reserved for the occasional ear which does not respond to more conservative management.

In the patient in whom good antibody titers are not present and who, for some reason, has not received proper antibiotics, the inflammatory reaction and extravasation proceed unchecked and produce a *purulent* type of effusion. A profuse cellular response is evoked, resulting in a marked thickening of the epithelial lining of the eustachian tube and, therefore, an obliteration of its lumen. As a result of the tubal obstruction, the secretions in the tympanic orifice of the eustachian tube, formed by the goblet cells and mucous and serous glands, flow in a retrograde direction into the tympanum. The mucoperiosteum of the middle ear becomes markedly hyperplastic and infiltrated with inflammatory cells, and the tympanum fills with

an effusion. Spontaneous rupture of the tympanic membrane occurs, or myringotomy is performed in this instance to give relief of pain and provide drainage of the purulent effusion. Since the patient usually seeks relief of pain or control of the otorrhea, his condition is not likely to be disregarded, and the customary treatment for acute purulent otitis media will be adequate to eliminate the disease.

Now let us examine the most frequent middle ear effusion encountered in private practice, the *mucopurulent* type. If inadequate therapy is given or treatment is prematurely interrupted, or if the patient gives a weak immune response, subsidence of otalgia occurs without sterilization of the tympanum and without drainage of the fluid from it. The smoldering subacute inflammation continues and stimulates the development of goblet cells and glandlike structures in the mucoperiosteum[12] which pour their secretions into the middle ear. Certain glycoproteins contained in these secretions and in the ground substance of the mucoperiosteum of the tympanum may exude into the lumen and contribute to the high viscosity of the fluid. Bacteria present in the fluid slowly multiply and induce a continued infiltration of neutrophiles. Thus there is insidiously produced the highly viscid secretion which is characteristic of the mucopurulent category.

We readily agree that some patients with a mucopurulent effusion show an allergic diathesis, including a positive family and personal history of allergy and recurrent episodes of rhinosinusitis. Nasal findings frequently include pale hypertrophic nasal and sinus mucous membranes, profuse nasal secretion and diffuse lymphoid hyperplasia of the nasopharynx and oropharynx. These upper respiratory tracts are very susceptible to infection, which spreads to involve the epithelial lining of the sinuses, eustachian tubes and middle ears. The infection causes superficial accumulation of lymphoid elements in the nasopharynx and undoubtedly produces stasis of those lymphatic efferents which drain the tubo-tympano-mastoid structure.

The evidence presented in these studies suggests that when these allergic patients with superimposed infection are first seen, viz., in the acute or subacute stage, therapy should be directed to the control of the inflammatory process of the middle ear and the superimposed disease in the nasal fossae and sinuses. After control of the infection, every effort ought to be made to discover and remove antigenic factors which are contributing to the suspected allergic state. If a state of hypersensitivity remains uncontrolled, a combination of a broad-coverage antibiotic and a corticoid may be prescribed for one week and the corticoid alone in decreasing dosage for a second week.

Occasionally it is necessary to request the assistance of an allergist, or an otolaryngologist who is skilled in allergic techniques, in investigating hypersensitivities in a comprehensive manner.

It appears inadvisable to us to perform repeated myringotomies in these allergy-suspect individuals. An initial incision and aspiration should be performed for drainage and diagnostic purposes shortly after therapy is begun. Later, occasional strategically planned myringotomies under general anesthesia should suffice to provide drainage and the restoration of hearing.

In those patients with persistent mucopurulent middle ear effusions which do not respond to medical management and aspiration, we *can* understand the rationale of inserting an indwelling catheter into the middle ear. In this instance there are believed to be marked

changes in the mucoperiosteal lining of the middle ear. In order to prevent irreversible damage to the middle ear structures, continuous external drainage must be provided until the provoking factors are removed and the soft tissues return to their normal state. This procedure has defects, including the tendency of the catheter to become dislodged or obstructed, and the great difficulty in evacuating the viscid secretion through the perforation by inflation or aspiration. Nevertheless, the alternative at this time is repeated myringotomies under general anesthesia, and we submit that the former is the less traumatic procedure.

We believe at this time that mastoid surgery is not ordinarily indicated for these individuals. Simple mastoidectomy does not remove the two obvious and most likely sources of the effusion, viz., the mucoperiosteal lining of the middle ear and the epithelium of the tympanic orifice of the eustachian tube. As long as these suspected primary sites of disease remain inaccessible, we accomplish little by destructive mastoid surgery.

We suggest the following regimen in the case of patients with mucopurulent effusions:

1. In addition to the usual ear, nose and throat examination, obtain roentgenograms of sinuses, audiologic work-up, eosinophile count of the peripheral blood and culture of the nasal fossae.

2. Give tetracyclines orally, 250 mg. every six hours, or, when these antibiotics are not tolerated, inject procaine penicillin, 600,000 units, and streptomycin sulfate, 0.5 gm., daily for two days prior to surgical operation.

3. Under general anesthesia, perform myringotomy, using some form of magnification to permit more precise examination. Aspirate the middle ear secretion into a collecting bottle and submit it to the laboratory for cytologic examination, bacterial culture and sensitivity tests.

4. When there is clouding of the sinuses on the roentgenogram, antral irrigation should be performed.

5. On the basis of the nasal and ear culture reports, continue the prescribed antibiotic or substitute that which is indicated. Maintain therapy for a period of one week.

6. If history, physical examination, ear smear, nasal smear or eosinophile count of the peripheral blood suggests an allergic factor, prescribe antihistamines and oral vasoconstrictors.

7. Recheck patient after one week and inflate the middle ear by continuous pressure politzerization. If fluid is present or there is persistent nasal infection, maintain patient on antibiotics or, where it is tolerated, change to sulfonamides to avoid complications associated with the prolonged use of tetracyclines. Give consideration to the use of corticoids in those individuals with an allergic diathesis.

8. In the event there is further accumulation of mucopurulent secretion and lymphoid residual is present, perform re-adenoidectomy under direct vision, myringotomy and aspiration and insert indwelling polyethylene tube for a period of one month.

9. If there is a history of repeated respiratory infection, initiate respiratory vaccine injections. Maintain patient on antibiotic and vaccine therapy until the ear has remained clear of effusion for thirty days.

10. Instruct patient or parent that the otologist is to be consulted on the first day of any respiratory infection, at which time active broad-coverage anti-

biotic therapy should be initiated in order to control any bacterial infection or to prevent secondary infection in the case of viral disease.

It is encouraging that more interest is being shown in this problem and that many reports of clinical observations are appearing.[1,3,5,14,26,27,34,35,37] In our laboratory progress is being made in the study of histopathologic changes associated with middle ear effusions and of the response of effusions to the action of various enzymes.

As is true for most disease entities, we shall arrive at a complete understanding of middle ear effusions and their specific prophylaxis and therapy only after we more thoroughly understand the etiologic factors and pathologic mechanisms involved.

We wish to express our appreciation to Dr. Gordon D. Hoople for stimulating our interest in middle ear effusions, to Dorothy L. Baldwin for her assistance in the secretarial phases of the project, to Nancy Hellman for editorial assistance, and to Marilynn Harris for artwork.

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DISCUSSION

OLIVER W. SUEHS, M.D., Austin, Texas: I am in full agreement with Dr. Senturia's conclusion that the microscopic examination of effusions provides the best data available for grouping effusions into meaningful categories.

Although the chemical analyses are most interesting and add to our general knowledge of these effusions, one must conclude that at the present time they provide no additional data of practical value in determining the nature of the fluid or in planning treatment.

It has been shown by Cantarrow and Trumper and others that the protein content of transudates and exudates in various parts of the body can vary tremendously because of variations in the intensity of the inflammatory process and variations in capillary permeability.

If the effusion has existed for some time, water may be resorbed more rapidly than solids, resulting in a slowly increasing concentration of protein which may eventually approach, or even exceed, that of true exudates, as shown by Dr. Senturia's work.

In the small series of protein determinations I have done, the protein content of serous fluids varied from 1.25 gm./100 cc. in a case of one week's duration to 7.2 gm. in one of three months' duration. I would like to ask Dr. Senturia whether he has found any correlation between the amount of protein and the duration of the disease.

It was interesting to note that only 11 of the 202 smears examined showed a single eosinophile in the entire slide. I have had a similar experience. This finding, however, must not be interpreted as precluding an allergic origin, although allergy has not been found to be an important exciting cause of effusion in my series of cases. We know that

allergy does predispose the individual to recurrent infections and, therefore, must be taken into account in the recurrent cases.

I wish to call your attention to the high percentage of positive cultures in both the serous and mucopurulent types of fluid in Dr. Senturia's study. Years ago, when we first became interested in this subject, we accepted the statement of previous authors to the effect that the fluid was sterile, and hence had very few cultures done. Upon reviewing my records of the past two years, I found that 86 per cent of my cultures were positive for one or more types of bacteria. How many of these represent contamination from the external canal, I am not prepared to say.

Most authors, in writing of secretory otitis media or middle ear effusions, have not included the category of purulent otitis media in their classification, but refer to the clinical types of "serous" and "mucous." According to Dr. Senturia's classification, it would seem that many of those cases we have termed "mucous" were in reality "mucopurulent," as they contained large numbers of neutrophiles. I find it somewhat confusing to think of acute purulent otitis media as a type of effusion, because the clinical picture is so different from that of secretory otitis media. There is no denying, however, that many of these cases, especially in children, represent aborted acute middle ear infections that would have become classical suppurative otitis media had their clinical course not been altered by antibiotics.

Dr. Senturia's concept of the pathogenesis of middle ear effusions is logical for those of inflammatory origin, but it does not encompass the serous effusions that are due to mechanical blockage or malfunction of the eustachian tube.

The regimen of treatment as outlined by Dr. Senturia should result in a satisfactory percentage of cures, because he correctly places emphasis on the diagnosis and treatment of the underlying cause of the tubal obstruction.

I agree with his statement that indwelling polyethylene tubes need not and should not be used routinely, but should be reserved for the chronic and recurrent cases of effusion. Some ears tend to extrude polyethylene tubes faster than others. Unfortunately, they are extruded prematurely or become obstructed most often in those cases in which we would like them to remain the longest; namely, the "glue type" ears.

I would like to ask Dr. Senturia whether he means that he continues antibiotics for a month after the ear is free of fluid, and, if so, in what dosage?

Dr. Senturia and his staff are to be congratulated on their important contribution to this challenging problem. It has been a privilege to discuss his paper.

GORDON D. HOOPLE, M.D., Syracuse, New York: This report is a continuation of the work presented by Dr. Senturia and his group in San Francisco in the spring of 1958. This group presents some additional information about the cellular, chemical, and bacteriologic findings of all middle ear effusions.

In discussing their paper in San Francisco, I said that I hoped that the work would be continued. This has been done, although even this is not a final report.

In the main, I am in agreement with the findings presented but would beg to differ a little in regard to some of the conclusions drawn and the treatment offered. Their work leads these authors to agree that "a microscopic examination of effusions provides the best data available for grouping effusions into meaningful categories." In San Francisco I begged Dr. Senturia and his group not to use the word "mucopurulent" in describing one class of middle ear effusions. I have asked him in a private communication not to do so, but he wishes to stick by this nomenclature. If he does, I can only add the warning that this does not mean what mucopurulent has meant to most of us in the past.

At one place in the paper the statement is made that the review of the evidence failed to indicate that allergy was an important factor in the etiologic findings. However, later in the paper the amount of anti-allergic medication advocated and the importance of the proper allergic management are so stressed that one feels that they should qualify this statement. In my hands this is certainly true.

I am puzzled about the bacteriologic results reported in this series. In essence, the percentage of the reported positive cultures was the same whether the effusion was purulent, mucopurulent, or serous. (There is a small difference in percentage between the serous and the purulent, but this is hardly enough to talk about.) Unless all of these cases were in children and unless they were receiving antibiotics, it is very difficult for me to understand these bacteriologic findings. They are at variance with past bacteriopathologic thinking. I would suggest using the same

technique from a bacteriologic standpoint on one hundred normal ears and making a report of these findings.

A goodly proportion of the paper is devoted to treatment. One must always remember when therapeusis is mentioned that "what is one man's meat is another man's poison." Some of the procedures that are advocated, in my opinion, are unnecessary. For instance, there is broad antibiotic coverage advocated for a period of three to four days following myringotomy. The number of times that I have opened drums for middle ear effusions is somewhere between 5,000 and 10,000, and in only two instances has a purulent discharge arisen where previously there was none. I am sure that three to four days of antibiotic coverage is not necessary. I am reasonably sure that Dr. Senturia does not need to worry about an overuse of the insertion of indwelling catheters. As a matter of fact, it might be wise to recall that when I presented my first paper on this subject in 1942, I said that in 50 per cent of the cases no myringotomy is necessary. Good medical treatment and good inflation clear this number. A high percentage of the ones that eventually come to myringotomy require only one such opening for relief of the condition. The use of indwelling catheters should be reserved, of course, for the occasional refractory case. And, I hasten to add, the number of refractory cases will be reduced almost to zero if proper allergic management is instituted. I have used an indwelling catheter only once.

I cannot see the necessity for giving a general anesthetic for opening fluid ears. It is true that I very often have opened ears at the time of tonsillectomy and/or adenoidectomy, but to do it as a routine procedure is entirely unnecessary in my opinion.

I cannot agree that there is a great increase in the incidence of these conditions. In my first paper, I reported that they constituted 4 per cent of an average otolaryngologist's office practice. I do not see any material change in this percentage. I will agree that there is an increased awareness of this condition.

The authors make one statement to which I would give hearty endorsement. The statement is, "We shall arrive at complete understanding of middle ear effusions and their specific prophylaxis and therapy only after we more thoroughly understand the etiologic factors and pathologic mechanisms involved." Finally they add one sentence which I think is the most important of the whole paper: "In our laboratory progress is being made in the study of histopathologic changes." Since my war experience, when I had the opportunity to examine the mucosa of thousands of middle ears due to the fact that there were so many blast injuries to eardrums, I have felt that the character of the mucosa of the middle ear and eustachian tube would give us the answer to the reason why in some ears effusions were present and in others, they were not. I will await with eagerness their report on any histopathologic studies. I am sure that some ears by Nature are given to effusions more than others. Also, the anatomical arrangement of the range of the mucous membrane in the eustachian tube is an important factor. Howard House and his group have demonstrated this with their study of tympanograms.

I congratulate this group on their excellent report and shall await their further investigations with great anticipation.

DR. SENTURIA: I thank the discussants. We were indebted to Dr. Hoople for his suggestions, and when he wrote me of his impressions regarding the mucopurulent category, we held several sessions with our research group in an effort to find some other term which might fit the classification. We realized then more and more that the future would probably set the terminology for us, and so for the moment we are continuing the mucopurulent type in the classification. I have the impression, although I do not have sufficient evidence, that these various categories are merely stages in the inflammatory disease. I would not doubt that at one point there is tubal obstruction, but the epithelium of the eustachian tube, having great regenerative power, quickly recovers but leaves the middle ear with a smoldering disease. In this state we have then a subacute otitis media. However, since we do not have proof for this we are not willing to make such a classification.

The problem of allergy is always with us. After reading Dr. Hoople's letter, I re-examined the original manuscript and I realized that I had overemphasized the allergic concept in writing the paper. I truly do not believe that many of our cases fall into the category in which allergy is a primary etiologic factor. We do not believe that allergy plays an etiologic role in the causation of the middle ear effusion. By this, we do not mean to minimize the importance of the allergic diathesis in the individual case. I hope that this concept is understood.

We certainly do provide our patients with antihistaminic therapy, but if antihistaminic therapy is substituted for antibacterial therapy, I think we fail in the proper treatment of the patient with the serous or mucopurulent type of effusion.

The bacteriologic findings disturb me as much as they do Dr. Hoople. I frankly do not believe that the incidence of positive cultures should be so high in the serous category, because I believe that this is a nasopharyngeal disease which is reflecting itself in a back pressure into the middle ear. This is a much different stage of the disease. In fact, we have all seen effusions of a serous nature in malignancy of the nasopharynx, in choanal polyps, and in various other conditions. When we analyze them chemically, in a few cases we find that they do not differ very much from the so-called serous otitis media which you and I have been seeing as a middle ear effusion.

The matter of treatment, of course, will be interpreted in many ways. Again I feel that we have an incipient infection in the serous category, and that it would be safer to treat these patients for a short time with antibiotics, but it certainly is not necessary. Several of my patients developed purulent otitis media secondary to myringotomy, and following this I began treating them with antibiotics. I would certainly agree that the incidence of secondary infection is rather low, and I would not disagree with anyone who wished to avoid this form of therapy.

I have been impressed with occasional reports that have come to me which indicated that some men were treating 200 and 300 patients with indwelling catheters in a single year. Now I may have been misinformed, but I observed a similar enthusiasm in the St. Louis area for indwelling catheters; men were reporting large numbers of them when I was inserting one, two or three a year. I think that Dr. Hoople and I are, therefore, in agreement that a catheter should be used in a properly selected patient.

I am much more insistent regarding general anesthesia. I think that one cannot evacuate a mucopurulent secretion from the middle ear without a general anesthesia if one is to avoid trauma to the medial tympanic wall and to the tympanic membrane. It is difficult to aspirate the thick, inspissated secretion, and I feel strongly that adhesions and severe secondary reactions following the trauma occur only when the mucoperiosteal lining of the middle ear is roughly handled as is often necessary when the procedure is done in the office, without anesthesia and without magnification.

I would certainly agree with Dr. Hoople that the increased number of cases we now see may be due to a greater awareness and better diagnostic equipment, but I have some reservation regarding this matter. I am impressed with the fact that more and more patients are receiving inadequate antibiotic therapy, and I think that we are therefore seeing smoldering middle ear diseases as a result of it.

I assure you that within a short time we shall have a report on the histopathology of the middle ear. All the serial sections are now completed, and we shall have more information in this regard in the near future. I, too, am hopeful that this will contribute to our knowledge.

In the matter of the duration of the disease (Dr. Suehs asked about this), we did not have the opportunity of correlating the chemical findings with the duration of the disease in our human subjects, but we were able to do it in our experiments on dogs. This is being reported. We find no correlation between the duration of the disease and the chemical constituents.

Tubal obstruction has been touched upon. I think that it is not an important factor in any but the suppurative cases. I believe that concept which I have suggested to you covers the entire field.

THE ROLE OF THE OTOLARYNGOLOGIST IN BRONCHOESOPHAGOLOGY

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THE development of the subject matter referred to in the title of this paper was suggested some months ago by Dr. Dean Lierle. The question of the role of the otolaryngologist in bronchoesophagology arose during a discussion in the Residency Review Committee for Otolaryngology while evaluating residency programs. The Committee is composed of representatives of the American Board of Otolaryngology, the American Medical Association, and the American College of Surgeons. It reviews with great care the residency programs throughout the country and recommends approval, provisional approval, or disapproval of programs to the parent organizations. The Committee may also point out to the head of a department the weakness of a specific program in an effort to improve the quality of teaching and education in the specialty. The wide variation of strength and weakness in bronchoesophagology in the programs throughout the country is very apparent when one compares statistics of endoscopic procedures performed by the staff and residents of different institutions. Reasons for this great variation are not difficult to find if one is satisfied with the usual cliches: "The thoracic surgeons have taken over bronchoscopy." "The gastroenterologists and the gastroscopists are doing the esophagoscopies." "The men in the tuberculosis sanatoriums are doing their own bronchoscopies and bronchograms."

But are these real reasons or merely rationalizations? Or worse, are these excuses? Does the otolaryngologist really have a role in bronchoesophagology? Is he interested in such a role? And conversely, an even more significant question which we should add but were not asked, "Does the bronchoesophagologist have a place in modern otolaryngology?" An honest self-appraisal and introspective search might help us find the answers to some of these questions.

Bronchoscopy and esophagoscopy are examinations that were developed by otolaryngologists. These specular examinations extended the fields of visual inspection through the oral cavity, an area anatomically familiar to the specialists in this field. The training the otolaryngologist receives in monocular vision prepares him for visual interpretation of the small endoscopic field seen through the long tubes required for bronchial and esophageal studies. Furthermore, the manual dexterity necessary for manipulation of endoscopic instruments is part of the daily routine training of the otolaryngologist. Thus, historically and by means of basic training, the otolaryngologist starts with a technical advantage in performing endoscopic examinations and in doing therapeutic surgical endoscopy. Yet, the changing picture of medicine and surgery has resulted in progress that has exerted great influence on the borders of the specialties. Two generations ago the specialty of sino-respiratory-pulmonary diseases represented a clinical

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division in medicine. It was a forerunner of the otolaryngology of thirty-five years ago. The field evolved into ear, nose and throat as the association with diseases of the chest decreased. Then Chevalier Jackson and his co-workers (Clerf, Tucker, C.L. Jackson), Mosher and his group, and the European laryngologists and endoscopists developed a specialty of great strength and importance *within* otolaryngology. But advances in anesthesiology, thoracic, pediatric and plastic surgery and phthisiology again have changed the borders of specialization; now surgeons and internists who had looked with much skepticism on the field of endoscopy suddenly find great need for its procedures and information. The tracheobronchial tree and esophagus suddenly have been rediscovered. We now see confirmation of the work of the otolaryngologist pioneers in the surgical, medical and anesthesiological literature — sometimes this confirmation even appears as reports of supposedly new clinical entities.

This rediscovery is one of the reasons for our present dilemma. Endoscopy has graduated from a surgical rite to a useful tool that is a necessary complement of many specialties. New concepts of pulmonary physiology and pathology, esophagology and thoracic surgery, have developed so rapidly that only through daily contact with these fields does one have an opportunity to keep up with their language, literature and achievements. More and more we find that the significant research is being reported in meetings of internists and thoracic surgeons; and, possibly of greater significance, that endoscopic work published in journals of otolaryngology is buried and lost to the general literature of that subject.

Closely paralleling the advances in the fields of intrathoracic diseases in which we, as bronchoesophagologists, must be vitally interested are two other major changes within otolaryngology that have greatly influenced our specialty. The first is the stimulus and challenge of the advances in ear surgery that have drawn many to this specialty-within-the-specialty. The infectious enthusiasm of otologists in this new phase of hearing restoration is fascinating to watch. But there is little hope that any who become interested and proficient in the delicate techniques of ear surgery will return to endoscopic endeavors. As a matter of fact, for some of us "on the outside," as it were, it seems more and more as though otology has attained as isolated an existence as ophthalmology. One need only observe the change in the audience at an ear, nose and throat meeting that takes place between succeeding papers, one on stapes mobilization and the next on bronchial adenomas; it is similar to the substitution in a football game between offense and defense!

The second change in our specialty influencing bronchoesophagology is the expanding interest in neck surgery, particularly as it is related to malignancies of the sinuses, the pharynx and the larynx. This surgery requires a basic training in laryngology — one that general surgeons entering the field often fail to realize. This bridge of laryngology is, without question, a major link, if not the only one, between otolaryngology and bronchoesophagology. Endoscopic techniques and procedures and adequate operating room facilities are essential in laryngology. And it is just as essential that by definition, a service in laryngology must include the neck surgery related to the treatment of laryngeal infections, trauma and tumors. But here, again, we find that we must compete with the ear symposiums in ear, nose and throat meetings; and our contributions to progress in the field are lost in the maze of the literature on fenestration and stapes mobilization.

There is no reason to hope to influence the pattern of the first change. And why should it be so influenced? Otology is a field in its own right; its highly technical diagnostic procedures and infinitely meticulous surgical techniques have contributed function-restoring possibilities unthought of when major attention was directed toward handling the acute and chronic ear infections. There seems little reason to expect the man who devotes his time and energy to this work to be responsible for the management of the esophagus of the infant with an esophageal atresia.

Yet, in the second area, that of neck surgery, we find a reasonable, direct, and very necessary tie between otolaryngology and bronchoesophagology. From a clinical as well as an organizational standpoint there is every reason to solidify this association between otolaryngologists and bronchoesophagologists. Their scientific achievements and reports require the support of otolaryngology in the competition they face; but while the scientific aspects must speak for themselves, the organizational aspects within the hospital, the medical schools, the clinics and the medical societies face a mounting problem. Bronchoesophagologists must be active in otolaryngology circles, in thoracic surgical and medical organizations, in pediatrics, and in the endoscopic aspects of anesthesiology. Thus, while the role of the otolaryngologist in bronchoesophagology may be a small one, or even nonexistent for some otolaryngologists, for others it may be a complete scientific endeavor. And, for the latter, what are his otologic and rhinologic ties? If they are purely historic, they are scientifically worthless. If they may serve as a teaching and clinical bridge between otolaryngology and general medical and surgical problems, they must be maintained, supported, and urgently strengthened. Obviously, the problem is not alone the role of the otolaryngologist in bronchoesophagology, but the role of bronchoesophagology in otolaryngology, and, as a parallel, the role of the bronchoesophagologist in otolaryngology.

There are, of course, many reasons for the drift of the subspecialty of bronchoesophagology into specialties other than our own. In many areas the drift has been by default, with the need for availability of service unrecognized or the potentialities of the field little realized. The extreme example of this is the isolated eye, ear, nose and throat hospital. Another reason is that the thoracic surgeon logically wishes to examine the bronchi or esophagus prior to his surgical procedures. But development of medical and pediatric endoscopy by the otolaryngologist is of sufficient importance that the few cases "lost" to the thoracic surgeon are of little consequence. As a matter of fact, it would appear that there is a shift back toward otolaryngic endoscopy where the otolaryngologist has the desire and makes a sincere effort to assume the obligations as well as the privileges of this field. As an example, statistics of our clinic at The Children's Memorial Hospital show that during the past five years there was an average of 700 diagnostic and therapeutic procedures per year. These include the dilatation of lye strictures, the removal of laryngeal papilloma, and the routine bronchial aspiration of children with bronchopulmonary suppuration due to postoperative, neurogenic or inoperable bronchiectatic conditions. Included, too, are the fascinating and bizarre foreign-body problems, that still have a clinical attraction all their own. But they also include the management of conditions that ten to fifteen years ago were nonexistent. For example, during the past 12 to 15 years, Dr. Willis Potts and his group have operated upon approximately 175 infants with congenital esophageal atresia—most with the usual fistula, a few

without. The condition formerly was invariably fatal. Now the salvage rate is 70 per cent, with a 50 per cent over-all survival rate of the series. Truly a remarkable record, but endoscopic procedures are necessary in approximately half of the infants that survive, because of the anatomical configuration of the distal segment. Strictures, pulmonary complications and foreign bodies all require endoscopic management. We removed a foreign body, a button, from the ascending colon of one of these infants perorally with an esophagoscope; the colon was a transplant, of course.

Another lesion, the vascular ring, has also come to be recognized as a rather common clinical entity. The majority of the more than 40 infants with this condition operated upon at The Children's Memorial Hospital were referred to the endoscopic service from elsewhere for the diagnosis and treatment of a persistent croup or congenital stridor. Other conditions, such as the management of the pulmonary complications of fibrocystic disease of the pancreas and the diagnostic problems of lobar atelectasis or emphysema in the newborn, are phases of pediatric (otolaryngic) endoscopy. These provide a rich type of clinical material in the pediatric hospital or in the general hospital with an active pediatric service for the otolaryngologist properly equipped and interested. Similarly, in each of two endoscopic clinics, one in a general hospital and one in a university hospital, an average of 1000 procedures were performed per year over the past fifteen years in the Division of Bronchoesophagology of the Department of Otolaryngology. Obviously, here too, the potential for an intensely interesting clinical experience is available. A comment we have heard more than occasionally from an intern or resident is that after experiencing isolation from medicine in otology or plastic surgery, he welcomes the opportunity for the contact with general medicine and surgery afforded by bronchoesophagology. There is a greater opportunity to talk to colleagues about more major over-all patient problems and to participate with them in patient management.

What are our responsibilities and obligations if we wish to retain this field in the broad concept of otolaryngology? First, it would appear that we should recognize that this is a surgical specialty in which acute, urgent emergencies are not uncommon. Personnel and instrumentarium must be available. Hospitals should supply and maintain endoscopic equipment for respiratory emergencies with the same sense of obligation that they supply scalpels and hemostats and Thomas splints for abdominal surgical emergencies or fractures. And it is quite self-evident that this equipment should not be locked up somewhere with the only key in the pocket of the supervisor who leaves at 5:30 in the afternoon. But just as obviously, *we* must be available, or others will be. The otolaryngologist who makes himself "unavailable" at certain hours or on certain days will most surely lose the foreign-body work, as well as the routine diagnostic and therapeutic endoscopy, to the thoracic surgeon who can be reached when needed. And to those who would answer, "Well, I couldn't care less," we would say, then, that we should be realistic and change our training programs and our Board requirements, eliminating those relating to bronchoesophagology. But until we do, we must accept this surgical obligation as a part of otolaryngology.

This leads directly to the subject of the training of the otolaryngologist in bronchoscopic techniques. The Council on Medical Education and Hospitals, in its "Essentials of Approved Residencies in Otolaryngology," requires an "adequate experience in bronchoesophagology. . . ." Surely, this is a broad, flexible definition of a training requirement.

The Board requirements are, of course, more specific. The candidate must be proficient in the applied basic sciences of, among others, the throat, neck, chest and esophagus. Limited certification in peroral endoscopy may be granted a candidate after not less than one year of training in a hospital approved for endoscopic teaching. He must pass an examination covering the larynx, pharynx, neck, esophagus, stomach, tracheobronchial tree, lungs, mediastinum, and certain aspects of cardiovascular diseases as they pertain to peroral endoscopy. It would seem that training for either type of certification must include experience in the medical aspects of chest diseases, a rotation through thoracic surgery, possibly during the "surgical year," and some work in gastroenterology. On the other hand, possibly even more specifically, it would seem that the training requirements of the internist and thoracic surgeon permitted to do endoscopic work in an approved hospital should include a rotation through otolaryngology and bronchoesophagology that would provide experience in laryngeal pathology and a basic training in endoscopic instrumentation and techniques.

Training through "short courses" of two weeks to a month is often criticized. These do serve as a basis for further training and were never intended to substitute for a thorough, complete teaching program. Yet those of us who give such courses are always impressed by the way the thoracic surgeons who participate grasp the concepts of the program, whereas to our otolaryngologist colleagues many phases of the course seem entirely foreign and new.

Our second obligation if we wish to retain bronchoesophagology as a part of otolaryngology is to recognize and respect the surgical aspects of the field. Years ago an objection or contraindication to bronchoscopy was that patients bronchoscoped occasionally developed diphtheria! Obviously, contamination from patients previously scoped who were diphtheria carriers was responsible. But the fact that we work through a nonsterile field, the mouth, should not make us less aware of the possibility of cross infection through faulty techniques of surgical cleanliness. The cursory washing of hands and the careless sterilization of instruments can hardly be considered surgically correct in spite of the contaminated field through which the scope must pass. Bronchoesophagology is a surgical specialty; procedures and techniques should be so considered. The otologist realizes the value of strict asepsis; the principles of surgery must carry over into the endoscopic operating room. The many severe pulmonary diseases in which a bronchoscopic examination is a part of the diagnostic work-up make it mandatory for us to be surgically clean. The procedures should be under recognized operating room conditions, with operating room supervision and adequate nursing help. But we must live up to what we are asking. When the endoscopic procedures are performed in the outpatient department, there is a great tendency to reduce vigilance and cut corners by breaking technique. Surely one cannot expect the nurses to have much respect for the procedure if the attending men or the residents carelessly contaminate the instrumentarium; or, even worse, if the attending men and residents smoke in the room! Such glaring lack of surgical discipline can only lead to justifiable criticism and disrespect from our surgical colleagues and nursing personnel.

Our third obligation concerns endoscopic techniques. What is the indication for the procedure? What information is requested? Where is the pathologic lesion located? Which lung? Which lobe? Which segment? Anesthesia must

be adequate to permit a careful examination. The open tube examination must be supplemented by the telescopic inspection of the segmental bronchi. The magnification afforded by these instruments is as necessary as magnification in modern ear surgery; and precision here is just as important. Furthermore, the report should be written with an anatomical accuracy on the level of the needs of the surgeon who must rely on the description of the most minute findings. A segmental localization of pathologic changes is exceedingly important in these days of segmental surgery. In bronchogenic carcinoma, a positive biopsy or smear is not sufficient information; what is the cord motility? What is the character of the carina? What is the exact location of the most proximal evidence of the lesion? And in esophageal carcinoma, has the tracheobronchial tree been inspected for evidence of tumor invasion? The percentage of positive bronchoscopic biopsies in patients with subsequently proven bronchogenic carcinoma is of importance. Figures of 75 per cent to 80 per cent should be achieved, whereas figures of 90 per cent, or better, by cytologic examination of sputum as an alternative should be analyzed. In a recent panel, this latter figure was given to stress its superiority over bronchoscopic biopsy techniques; then, almost as an aside, it was stated, "Of course, this does not include the silent lesions." Our obligation is to approach the 80 to 90 per cent figure possible by precision techniques when the large group of silent lesions is removed from the analysis.

In addition to the careful preoperative study of the patient and his disease in order to obtain the most information through the endoscopic procedures, there is the obligation and need to develop a superior endoscopic technical skill. This assumes an intimate knowledge of the methods of the introduction of scopes into adults, children and infants; forceps manipulation; and foreign body and biopsy techniques. It should also include the various possibilities of endoscopic surgery involving upper lobe biopsy and aspiration, intrabronchial cardiac catheterization and endoscopic resection techniques. These procedures should be learned and rehearsed on anesthetized dogs. We must follow the example of the otologist, who gets his training in temporal bone surgery in the laboratory and is familiar with the anatomical landmarks when he reaches the operating room. Only after such laboratory training and self policing through constant practice can we develop an undisputed place for the otolaryngologist in bronchoesophagology.

Now to reverse the concept of obligation: if otolaryngologists wish to retain a role in bronchoesophagology, what are the responsibilities of the various organizations that represent otolaryngology? First and foremost is the realization that bronchoesophagologists have strong ties with general and thoracic surgery, pediatrics, and internal medicine, including diseases of the chest and gastrointestinal tract. We must have the opportunity to meet with these groups. Furthermore, it is essential that those responsible for bronchoesophagology on otolaryngological services attend meetings of chest physicians and participate actively in their clinical and research programs. The American Bronchoesophagological Association might wisely meet with other groups from time to time, particularly since there is so great a competition for time between the otologists in the Triological in the morning and the endoscopists in the afternoon. The American Bronchoesophagological Association did meet with the American Medical Association and the American College of Chest Physicians a number of years ago in order to be better recognized in these groups. The meeting had

the largest attendance of any bronchoscopic society meeting held up to that time—but the member attendance was low. Yet the discussions were most stimulating because all aspects of a subject—surgical, medical, radiological — were represented, rather than only the otolaryngic approach to a chest problem.

An even more urgent obligation of otolaryngology and bronchoesophagology has been a subject of considerable controversy the past few years. If it is desirable to retain bronchoesophagology as a part of otolaryngology, it is imperative that we avoid a conflict of meeting dates between the Academy and the American College of Surgeons. Surgical ties of bronchoesophagology are constantly becoming stronger because of the expansion of the field of laryngeal and neck surgery. If otology—and ophthalmology—feel as strongly as we do that representation in the scientific and organizational meetings of this surgical policy-forming organization is desirable, every effort must be made not only to maintain, but to strengthen our position. We will surely weaken it if we are not represented by a section on otolaryngology along with those of obstetrics and gynecology, genitourinary tract surgery, orthopedics, and, recently, a section on head and neck surgery at national surgical meetings.

To return to the original thesis, it is apparent that there is an important role which the otolaryngologist can play in bronchoesophagology, provided he wishes to maintain this link with the broader aspects of the practice of medicine. But it is useless to ask a man to become proficient in a field of medicine in which he has no interest; therefore, while this subspecialty has a place in otolaryngology, it is lessening in significance. It seems more and more evident that for many the responsibilities outweigh the advantages. Shall we continue our efforts to retain bronchoesophagology in otolaryngology when the only justification for the relationship is through laryngology? We can if we accept it as a surgical specialty of increasing importance in medicine, surgery and pediatrics. As such, its training programs must include surgical, medical, pediatric and radiological training in diseases of the chest. If we do not wish to retain this relationship, then residency and Board requirements should realistically reflect this attitude and remove this field from the training programs and Board examinations. However, the academic status of bronchoesophagology in the hospital and medical school training programs must have the support of a parent specialty—if not otolaryngology, then by design, the Department of Medicine, as at the Mayo Clinic; or by default, the Department of Surgery, as in some of the teaching centers not only in this country but also abroad.

In any eventuality, we must keep our own house in order. If we cannot do all the endoscopy, let us at least do the best of it. But in the selection of the endoscopist, be he an otolaryngologist, thoracic surgeon, internist or anesthesiologist, equal criteria of training and proficiency should prevail. The otolaryngologist receives special training in laryngology and diseases of the chest. In the same vein, the thoracic surgeon or internist should be required to participate in special training in laryngology and endoscopy. But whoever chooses the field or is assigned the responsibility to practice it, must have an adequate instrumentarium with suitable operating room facilities and help. He must have the support of his hospital and medical school, and the organizational support of his parent specialty. These prerequisites are essential to adequately discharge the obligations and benefit from the privileges of the clinical, teaching and research potentials of bronchoesophagology.

SURGICAL TREATMENT OF CANCER OF THE EAR AND TEMPORAL BONE

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MALIGNANT tumors of the auricle, ear canal and temporal bone comprise a unique group of new growths in a special sense organ. Their surgical management requires careful analysis of the type, position, and size of the tumor and its relationship to the vital structures in this area. The esthetic qualities of the pinna, the hearing and vestibular apparatus, the facial nerve, and, in the more extensive problems, the mandible, parotid gland, temporal bone and lateral neck, must be equated. A division of the cancerous tumors into three groups adds some clarity to the management and facilitates statistical analysis. These categories are:

1. The auricle
2. The ear canal
3. The temporal bone

These three principal groups may be further subdivided into the type, site, and size of each tumor in each category. It is obvious that the larger neoplasms in any one of the groups may involve all of these structures and extend into the surrounding tissue.

Because of the uniqueness of their biological processes, thirteen neurogenous tumors about the ear and seventeen melanomas of the ear are analyzed in a separate report to follow.

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AURICLE

Incidence

Cancer of the external ear is not common. Approximately 90 per cent of the skin cancers of the body occur on the face and neck. Six per cent of all skin cancers grow on the ear. The world statistics indicate that approximately 85 per cent of cancers of the ear are on the auricle, 10 per cent in the ear canal, and 5 per cent in the middle ear. In my particular series, which is a smaller and more specialized group, 44 per cent are on the auricle, 30 per cent in the ear canal, and 26 per cent in the temporal bone. This statistic is explained by the fact that cancers of the auricle in this city are treated by various groups of specialists. Twelve of the 13 cases studied were determinant. Eighty per cent of these tumors occurred in males, and 20 per cent in females, and 80 per cent occurred in the sixth and seventh decades of life.

Etiology

The etiologic factors are associated with the degenerative processes of advanced years and the local and chronic trauma sustained from sun, wind, chronic infection, chronic irritation, chronic eczema, psoriasis and lupus, and x-ray injury.

Diagnosis

The diagnosis is usually immediately apparent on gross inspection. The gross appearance of these neoplasms may be that of a small superficial tumor with

or without ulceration. Another variety becomes vegetative and papillary in quality, piling up on the ear in an exuberant mass. A third variety becomes infiltrative, ulcerative and destructive. This latter group may destroy the entire auricle and extend into the parotid gland and mastoid bone. The majority of the tumors occur on the helix and antihelix with a diminishing incidence on the concha, lobule, tragus and antitragus.

In the differential diagnosis, the various keratoses, chronic dermatitis, eczema, lupus, psoriasis, cysts and benign tumors must be excluded.

Histopathology

The microscopy is always established by preoperative biopsy. The majority of the tumors of the external ear are squamous cell cancer. In the series, 62 per cent were squamous and 31 per cent were basal cell types. One was interpreted as fibrosarcoma. One patient had experienced chronic trauma from a plaster head cast for several months prior to the development of cancer. Fifty per cent of the patients had had some previous type of treatment; five of these had been exposed to irradiation and one to surgical excision, without success.

In two patients, clinical metastasis was present. One patient had metastasis in the postauricular lymph nodes, and the other had multiple metastases in the superior deep cervical and the infra-auricular lymph nodes. The cancer in the first instance was 2x2 cm. and was located on the superior helix, and in the second instance it was 1x1 cm. and was located on the concha near the lobule. In the second instance, the patient succumbed to his disease.

Treatment

All of these lesions were treated by surgical intervention. One small tumor underwent partial auricular resection and V-closure. Three tumors in the region of the helix underwent resection and repair by postauricular pedicle flap. Five tumors in the region of the prehelix and concha underwent partial resection of the ear, partial parotidectomy and radical neck dissection for metastasis. None of these had a local recurrence.

Rehabilitation of the ear by V-closure causes a natural diminution in its dimensions and creates a tendency to cupping. The use of the postauricular flap has significant advantages in recreating the helix even though it is a two-stage procedure. The free full-thickness postauricular skin graft for restoration in the region of the prehelix and concha has proved most helpful. When the skin on the back of the auricle is uninvolved, and the tumor block includes skin of the concha and associated cartilage only, the rehabilitation is carried out by the application of the full-thickness skin graft directly over the wound on the inner aspect of the ear. It is held in position with a stent. In the more extensive cases requiring total ablation of the ear, the wound is covered with a free split-skin graft. The simplest and most acceptable type of esthetic restoration after total auricular resection is by prosthesis.

Results

The salvage rate in these 12 determinant cases of cancer of the auricle is 92 per cent, with 1 death being reported.

EAR CANAL

Cancers of the external ear canal are rare. In the past, they have presented a difficult problem in adequate surgical extirpation because of the anatomy of the canal, the awkwardness of technical management, the proximity of the organs of hearing and balance, the seventh nerve and the head of the mandible.

The cases in this category were divided into three groups in respect to the size and position of the primary cancer and the treatment carried out. These groups are:

1. Cancer of the membranous external canal in which soft tissue extirpation and skin grafting were employed.

2. Cancer of the external canal involving the membranous and bony portions, requiring excision of the lining of the canal and radical mastoidectomy.

3. Cancer of the canal that had extended to the mastoid or parotid or eustachian tube area, or auricle, and where a more extensive extirpation was indicated.

Twelve of 13 cases studied were determinant. Sixty per cent of the individuals were males and 40 per cent females. Eight individuals were over 60 years of age, with a range from 41 years to 85 years. The average age in this group was less than that for the group with cancer of the auricle.

Etiology

Chronic otorrhea and chronic dermatitis of the external ear canal have been associated with malignant tumors at this site in a high percentage of the cases. Thirty-eight per cent of the individuals in this group gave a history of chronic suppurative otitis media or external otitis.

Diagnosis

The majority of individuals with cancer of the ear canal complain of otorrhea, pain, bleeding, ulceration, and diminution of hearing. If the cancer has extended into the middle ear, facial nerve paralysis, vertigo, and roentgenographic evidence of bone destruction may be apparent. In the differential diagnosis, external otitis, furunculosis, eczema, fungus disease, chronic suppurative otitis media, mastoiditis, and presence of a foreign body must be excluded. When the symptoms do not respond to treatment, diagnostic biopsy should not be delayed.

Histopathology

The vast majority of the cancers of the ear canal are of the squamous cell type. In this series, 78 per cent were squamous cell carcinoma, 15 per cent adenocarcinoma, and 7 per cent basal cell carcinoma.

Metastasis to the regional lymph nodes was present in 17 per cent. One case manifested pretragal and parotid metastases, and in another there was involvement of the submaxillary lymph nodes.

Treatment

The surgical technique in cancers limited to the membranous external canal where bone is not involved consists of a wide resection of the entire membranous canal and dressing the wound with a free split-skin graft held in position over a stent.

Cancers involving the membranous and bony portions of the external canal are best handled by extirpation of the soft and cartilagenous tissues of the canal in continuity with the bony encasement and tympanic membrane. This technique requires special consideration in the preservation of the facial nerve and in planning an adequate cancer operation. An augmented postauricular incision with transconchal and tragal extension gives an adequate exposure to the ear canal and mastoid bone. After a modified radical mastoidectomy with anterior extension toward the zygoma has been carried out, the membranous and bony canals are fractured and removed by appropriate osteotomes.

As the bony fracture cannot be controlled by this method, cracks into the ear canal, injury to the facial nerve, and removal of an inadequate specimen are constant sources of concern. Dr. Edmund Prince Fowler, Jr., suggested that the perforating burr be used to make holes that would indicate the intended fracture line in the removal of the specimen. This has been worked out on cadavers and has been tried on two patients; it has proved to be a definite advantage over the piecemeal resection or blind fracture. It is hoped that this improvement will be reflected in subsequent 5-year cure reports.

The operation has also been modified to include complete exposure of the seventh nerve from the fallopian canal in the middle ear to the stylomastoid foramen. Its course is followed into the parotid gland. A groove deep to the nerve is made with the burr from the external horizontal semicircular canal inferiorly to the digastric groove. The facial nerve is then reset into this deeper trough and bony encasement of the external auditory meatus is mobilized with a small burr. Deep penetration of the burr is necessary in the anterior superior portions of the middle ear and again inferiorly and anteriorly inferiorly toward the middle ear. The suture line of the tympanic plate anteriorly is drilled into the tympanum. A thin, sharp osteotome is then placed in these prepared grooves and the residual bony attachment fractured. The specimen contains the contents of the external auditory meatus encased in a membranous and bony canal with the annulus tympanium and drum at the inner level and the cut concha and tragus at the outer perimeter. The exposure of the seventh nerve has the advantage of preserving its integrity and also of adding 2 to 3 mm. to the depth of the bony dissection. This is usually essential in obtaining a satisfactory specimen. The postsurgical cavity is dressed with a free split-skin graft.

Results

Of the 13 cases studied, 12 were classified as determinant. One patient with a determinant case died of mesenteric thrombosis and gastrointestinal hemorrhage one year after surgical intervention, without any evidence of local recurrence of the cancer, and one follow-up was not informative. Both cases have been classified as determinant and as failures in treatment.

Four patients in which the cancer was essentially limited to the membranous external canal were treated by local soft tissue resection and skin grafting techniques. Two patients are dead of their disease, one is living with a probably incurable recurrence, and one is free of disease. There were no metastases in this group, and the 5-year cure rate is 25 per cent.

In the group (five patients) in which the cancer involved both the membranous and bony canals, two individuals had resections of the canal with radical mastoidectomy and are dead of their disease. Two individuals had resection of the ear canal and radical mastoidectomy, one supplemented with 7200r, and both are free of disease. One adenocarcinoma of the external ear canal (cylindroma) was treated with 3000r (1943) and with 5000r (1945) for recurrence. In 1946 a resection of the ear canal with skin grafting technique was carried out. In 1951 an augmented resection of the area with a partial temporal bone exenteration was performed. In 1958 there was a 0.5 cm. recurrence on the posterior wall that was treated by cautery excision. The course of this cancer has extended over fifteen years and it has remained localized. There were no clinical metastases in this group. The 5-year cure rate was 40 per cent. The addition

of bone surgery and the use of irradiation in one case may explain the increased cure rate in this small series.

A third group (3 cases) consisted of cancers of the ear canal that had spread to the mastoid process, middle ear, tragus, auricle, eustachian tube area or parotid gland. Two of the patients in this group manifested regional metastasis. These problems were handled by wide extirpation. One patient died of gastrointestinal hemorrhage. One individual died of extension to the base of the skull and brain. The one survivor had extended radical surgery and 5000r postoperatively. After a serious and protracted osteomyelitis (1950), a complete recovery resulted. The cure rate in this group was 33 per cent.

The over-all 5-year cure rate of cancer of the ear canal was 33 per cent. Seventeen per cent of the patients are living with recurrence, and 50 per cent are dead.

MIDDLE EAR AND TEMPORAL BONE

Cancer of the middle ear and temporal bone presents a difficult technical problem in extirpation and a grave prognosis. The surgical treatment has, on the whole, been piecemeal in type. The specialized organs and structures in this area cannot be salvaged, yet with freedom of activity, the *en masse* removal of the middle ear, mastoid, labyrinth, a portion of the petrous pyramid and soft tissues is associated with serious operative and postoperative complications. The excision of the tumor in some instances requires inclusion of the parotid gland, mandible, zygoma, temporal and masseter muscles, a neck dissection and resection of a portion of the dura. Removal of this additional tissue often gives better exposure to the wound, but increases the morbidity and detracts from the functional activity of the area. Ward,[3] Campbell,[1] and Parsons and Lewis[2] have pioneered significant work on resection of the temporal bone, and their reports indicated the feasibility of radical surgical intervention in this area. The report by Parsons and Lewis is fundamental and deserves special study by operators in this field. Our report deals with the extension and modification of technical procedures about the middle ear, mastoid and temporal bone.

This category includes 11 determinant cases in which the tumor arose in and involved the immediate area of the middle ear and mastoid structures. Eighty-one per cent of the patients were male and 19 per cent were female. Six were over 60 years of age, and the age group extended from 29 years to 84 years.

Etiology

Twenty-eight per cent (3 patients) gave a history of suppurative otitis media of 15, 20 and 40 years respectively.

Diagnosis

Pain was a significant aspect of the clinical picture in almost all cases. Bleeding from the ear canal and ulceration were common. Three individuals had facial paralysis. Two individuals had vertigo. Roentgenographic study of the bone was helpful in many instances but did not prove to be definitive.

Ninety-one per cent of the individuals had squamous-type cancer, grade *II* and *III*. Nine per cent (one patient) had an adenocarcinoma of the cylindromatous type.

It would appear that early diagnosis of tumors in this area is unlikely because of concealment and early paucity of symptoms and signs. As the tumor progresses in size, the pressure of its mass and the destructive qualities of its activity manifest themselves. Pain and head-

ache on the affected side are the most common complaints. Involvement of the ninth, tenth, eleventh and twelfth cranial nerves indicates extension into the base of the middle fossa and an incurable status. The transverse process of the atlas, the body of the atlas and axis, and the adjacent area of the occiput may also be destroyed in extensive tumors at this site. Extension into the neck along the eustachian tube and into the nasopharynx indicates inoperability. Extension to the dura is common in the later stages of the disease.

Neurogenous tumors consisting of glomus jugular, glomus tympanicus and paraganglioma at the base of the petrous, ganglioma and malignant neurilemmoma are not infrequent at this site. They will be discussed in a separate section, but must be included in the differential diagnosis along with cholesteatoma, osteoma, fibrous dysplasia, primary somatic tumors, hemangioma, metastatic cancer and vascular abnormality.

Treatment

Eight of the individuals in this series were treated upon previous occasions by irradiation and/or radical mastoidectomy. Four of the individuals had had multiple operations, with recurrence. Only three had been untreated.

One individual presented metastasis to the superior deep cervical chain.

The operation in all instances included a partial resection of the temporal bone. In one case, it included the major portion of the occipital bone and dura at this area. Seven individuals had an inclusion of a portion of the ear, the ascending ramus of the mandible, parotid gland, masseter and temporal muscles, and the upper neck.

The surgical technique consists of a direct lateral approach to the middle and posterior fossae and the base of the skull. The primary incisions create an ear flap which is transposed on a superior temporal pedicle, or on an anterior face flap. The excision is then extended into the lateral neck to the level of the carotid bulb. Further extensions may be carried out in conjunction with the classical lateral neck dissection.

The tumor in the region of the temporal bone and base of the skull is then circumvented by releasing the temporal muscle of the skull and performing an osteotomy on the zygoma, transecting the ascending ramus of the mandible and including the parotid gland, masseter muscle, posterior belly of the diagastric, stylohyoid, external and internal pterygoid muscles and sternocleidomastoid muscle. The common carotid artery at the level of the bulb and then the internal carotid artery, the ninth, tenth, eleventh and twelfth cranial nerves along with the sympathetic chain and jugular vein are exposed in the high neck and followed to the base of the skull. With these important structures under direct visualization, additional security is given to the technique.

The squamosa of the temporal bone superiorly and anteriorly is removed with rongeur. If the dura is tense, cerebrospinal fluid is withdrawn by a previously implanted plastic spinal fluid catheter,[2] or directly through the dura if the field is clean. This facilitates retraction of the temporal lobe and cerebellum and permits inspection of the petrous pyramid. Re-injection of the spinal fluid has not been found necessary.

The control of bleeding is an important factor in the progress of the operation. The sigmoid sinus, the inferior and superior petrosal sinuses, the internal jugular vein and internal carotid artery must receive special attention. Packing, tamponage, transfixion and coagulation

are frequently necessary. An ample supply of blood (3,000 cc.) should be on hand for adequate transfusion purposes.

At this stage of development of the operation, the petrous bone is fractured just lateral to the internal carotid artery canal. This fracturing may be accomplished by osteotomes or a rocking maneuver. The cavity is then dressed with a split-skin graft, and the face and neck flaps are repositioned.

Postoperative care consists of ample biotherapy and general supportive measures. An elective tracheostomy is essential for patients in the older age group and in cases in which the vagus nerve has been injured. Vertigo, nausea, vomiting, lassitude, cerebrospinal fluid leak, aspiration pneumonia, postirradiation necrosis of tissue flaps and bone, and meningitis may complicate the postoperative course.

Prognosis

The operative mortality in this series was 27 per cent. One patient died of meningitis and brain hemorrhage (14 days postoperative); one patient died of meningitis and pneumonia (12 days postoperative); and one patient died of hepatitis and pneumonia (2 months postoperative). Five additional patients died of their disease, two with local recurrence in the wound and in the neck, and three with intracranial extension. One patient was lost to follow-up and is considered dead of his disease. The over-all mortality is 82 per cent. This figure reflects three individuals whose disease could not be totally excised. The five-year cure rate is 18 per cent. The operation is associated with significant esthetic and functional disability. Improvements in technique and management in the past five years have added increased security to the operative and postoperative phases, and it is believed that the over-all salvage rate will be improved.

SUMMARY AND CONCLUSIONS

Malignant neoplasms of the ear are uncommon. These tumors are grouped into those occurring (1) on the auricle, (2) in the ear canal, and (3) in the middle ear and temporal bone. The vast majority occur on the auricle, with decreasing incidence in the ear canal and in the middle ear.

Occurrence in the male is significantly more common than in the female. The age group for cancer of the auricle is older than that for cancer of the ear canal or temporal bone.

Etiologic factors relative to the degenerative processes of advanced age and chronic trauma from sun and infection are often associated with tumors of the auricle. Thirty-eight per cent of the patients gave a history of infection of the external canal or middle ear in cancers of the canal, and 28 per cent gave a history of otitis media in cancers of the middle ear.

Diagnosis in respect to the auricle is usually apparent from the gross character of the tumor, being either a small nodular lesion, a fungating lesion, or an ulcerating destructive one. In the ear canal, clinical diagnosis is more difficult because of similarity to external otitis and chronic dermatitis. Diagnostic biopsies should not be unduly delayed in these instances. Diagnosis of cancer of the middle ear and temporal bone is usually delayed because of concealment and paucity of symptoms in the early stages. Roentgenography is of little assistance in the early phases. When essential structures and neighboring tissues are invaded, the disease is advanced, and the diagnosis is usually obvious.

Squamous cancer is the dominant type of neoplasm. Basal cell cancer is not uncommon on the auricle, and adenocar-

cinoma is less frequent in the ear canal and middle ear.

The surgical treatment of the auricle presents no particular excisional problem. Reconstruction, however, requires special planning. The ear canal is divided into the membranous portion and the bony portion. A new technique has been devised for treating cancer which has invaded the canal. The procedure accomplishes *en bloc* removal of the tympanum, bony and membranous element, and preserves the facial nerve. Cancers of the middle ear and temporal bone are removed *en masse* and the specimen may include the dura, parotid gland, ascending ramus of the mandible, temporal muscle, pterygoid muscle and lateral neck. This obviously formidable procedure has limitations in advanced cancer in this area, but has definite value in cancer limited within the bony capsule of the middle ear and temporal bone.

The biological behavior of squamous cell cancer in the ear indicates that 17 per cent of the cancers of the auricle, 17 per cent of the cancers of the ear canal, and 9 per cent of the cancers of the middle ear and temporal bone metastasized to the neck. Local recurrence was not a feature in the surgical treatment of tumors of the auricle, but in the canal and temporal bone became a dominant feature. Extension into the brain is not an uncommon consequence in cancer of the middle ear and temporal bone. Systemic metastasis was not observed.

Previous unsuccessful surgical treatment and irradiation occurred in 33 to 73 per cent of the cases and must necessarily reflect itself in increased mortality.

Postoperative irradiation was employed in two individuals who had extensive and what appeared to be incurable cancer originating in the ear canal. In one instance the tumor extended into the eustachian tube. Both of the patients are well beyond the five-year period, and although one developed a postirradiation osteomyelitis of the base of the skull, active for one year, re-evaluation of this modality as a further assist in the control of cancer at this site is indicated.

Two separate surgical techniques are evolving for cancer of the ear canal and cancer of the middle ear and temporal bone. Tumefactions limited to the canal do not require destruction of the facial nerve, labyrinth or cochlea. Tumefactions in the middle ear and temporal bone that have not dehisced the bony capsule require exenteration of the facial nerve, labyrinth and cochlea. When these tumors have extended beyond the capsule and invaded the dura, parotid gland or mandible but are still localized, an augmented operation including these structures may be applied with the hope of improved palliation and possible control. When the disease has gone beyond these limitations, control is unlikely.

A review of 12 cases of cancers of the auricle gave a 92 per cent cure rate; of 12 cases of the ear canal, a 33 per cent cure rate; and of 11 cases of the middle ear and temporal bone, an 18 per cent cure rate.

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DISCUSSION

JOHN S. LEWIS, M.D., New York: It is obvious that in such a short time, it is only possible for me to discuss in a general way this very broad dissertation on Cancer of the Ear.

It has been said that the only parts of the human body that are immune from cancer are the hair, the teeth and the nails. It is surprising that an organ affected so frequently by acute and chronic infections and irritations, as is the ear, is so rarely affected by cancer.

In my own experience, the classification presented by Dr. Conley as to anatomic sites of the primary lesions describes the most practical surgical classification. Ear cancer does not lend itself well to radiation, and the surgical attack with experience offers the best prognosis, especially for advanced disease. Morbidity is less and results with experience will justify the effort.

Two thirds of the cases of cancer of the auricle in my experience have been of the basal cell type. These are amenable to wedge or V excision when the helix is involved, or to wide excision and skin graft or rotated scalp flap at other sites. Cartilage is taken with skin. An infiltration lesion of the squamous cell type may require sacrifice of the entire pinna, while a fungating superficial lesion may be treated more conservatively. About 10 per cent of these cancers will metastasize to neck nodes and necessitate a neck dissection.

Cancer of the membranous canal is usually of the squamous cell variety, although adenocarcinoma arising from ceruminous glands, or melanoma may arise here. Wide excision of the entire membranous canal with a skin graft over a stent is the safest method of management. Involvement of the bony canal contiguous to the eardrum has been handled in an ingenious way by Dr. Conley. It may give 2 to 3 mm. of additional margin and spare the facial nerve, but the surgical margin, in my opinion, is in jeopardy. I would not feel upset in taking a wider margin by a temporal bone resection if the middle ear were free of disease, which so rarely happens. The method described by Dr. Conley would be excellent in a few highly selected cases with no infiltration and confronted to the ear canal.

I have confined my conservatism to the membranous canal and external ear. Prior to 1951 some 50 cases at Memorial Center in New York were treated by radical mastoidectomy and postoperative radiation. The survival rate of this group was less than 10 per cent. An approach was evolved by Parsons and myself to give a wide safe surgical margin. Once the bony canal and temporal bone are involved, a combined intracranial-extracranial *en bloc* resection of the temporal bone is required. About 50 per cent of my cases of advanced cancer of the ear canal and middle ear involving temporal bone have been radiation failures. Bleeding may be reduced considerably by utilizing a hypotensive agent such as Arfonad. A properly functioning malleable spinal puncture needle is a necessity to allow for the removal of enough spinal fluid to ensure an adequate petrous osteotomy, and temporomandibular joint and zygoma must be removed to ensure an adequate margin. Skin grafting over dura in the operative defect is usually successful, although gram negative infections with meningitis will occur in about 20 per cent of cases. Postoperative radiation, including supravoltage to areas of recurrences, has been disappointing, especially if dura or base of skull are involved. Aggressive surgical excision as a primary method of treatment, with radiation postoperatively to those with a questionable margin, gives the best hope for cure. My total experience would indicate an over-all salvage rate of 30 per cent in 3-year cures for those cancers involving the temporal bone, in which cancer is confined to the temporal bone and not already invading dura, brain and base of skull. As experience with the technique is gained, operative mortality and morbidity are reduced dramatically.

DR. HAROLD W. JACOX, M.D., New York: From a radiologic point of view, one can make the categorical statement that when cancer invades and destroys bone, it is next to impossible to get a cure by any form of radiation, conventional, deep therapy, orthovoltage or any supervoltage, radium or any other kind, because the osseous tissue has no ability to react to the radiation, as we find in well vascularized tissues. So we start out by knowing that radiation is not the method of choice in any of these lesions with the possible exception of small, skin-like cancers of the pinna.

As for being able to cure cancer in the middle ear or in the temporal bone by radiation alone, there is hardly any chance. The best method, it seems to me, is first the surgical approach, followed by intensive irradia-

tion to any of the cancer that may be left in the area involved. For example, Dr. Conley and I had a patient with a cancer of the temporal bone that was a radiation failure. This patient was treated on the betatron, 24 million volts supervoltage. He had a tumor dose of 6,000r, which improved his symptoms somewhat. Two and one half years later he had a recurrence and had retreatment with the betatron to the point of 7,000r, tumor dose. Six months later Dr. Conley removed the entire temporal bone, which was no mean feat in this case. He went along beautifully, even though he had all that heavy radiation with supervoltage, but histologically there were plenty of active cancer cells in that temporal bone after a total tumor dose of 13,000 roentgens over a period of two and one half years. That speaks for itself, it seems to me: you cannot cure this cancer with radiation.

So I plead for cooperation between the surgeon and the radiologist, and hope that by the method of using postoperative irradiation in those cases in which it is probable that cancer has been left behind, better results will be obtained by that combination of surgical and radiation techniques.

DR. CONLEY: In summary the picture appears to point up like this: If there is a cancer of the ear canal, of the middle ear or temporal bone, the case can best be treated by a comprehensive surgical attack, not radical mastoidectomy but a comprehensive block resection when possible. If this is not successful according to the examination of the specimen, then the patient should be considered for postoperative irradiation.

A LACRIMAL SUTURE-PROBE

AARON A. MANNIS, M.D.
CHULA VISTA, CALIFORNIA

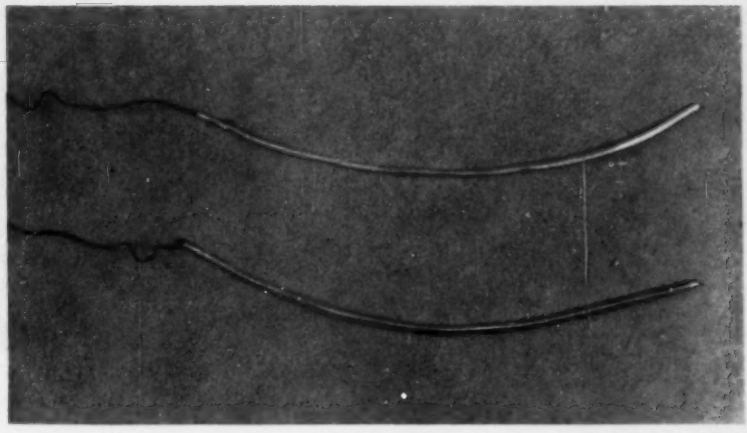

FIGURE 1.

A SIMPLE instrument has been found helpful in threading the lacrimal passages with a suture in the treatment of nasolacrimal duct obstruction, especially in children who have failed to respond either to irrigation or to repeated probings, and also in the repair of lacerations of the canaliculus.

I first used this instrument in 1954 to repair a lacerated canaliculus in a 4-year-old child, after discovering that Veirs' no. 18 special lacrimal needle[2,3] was too large in this case. Ellis' lacrimal probe-needle[1] was subsequently introduced in 1956. However, I feel that this new instrument has several advantages over both the others. I extended its use to cases of epiphora and chronic dacryocystitis secondary to obstruction of the nasolacrimal passages, having used it successfully in four such cases in the past five years in children, and also in one young adult, making a dacryocystorhinostomy unnecessary. It was unsuccessful in two adults with chronic obstruction complicated by mucocele formation.

The suture-probe (fig. 1) consists simply of half a Bowman's probe broken from its soldered connection to the fingerplate, hammered at this end as flat and thin as possible, then folded over a suture, hammered back into position and polished smooth. As shown in the illus-

Presented as a *New Instrument* at the Sixty-Fourth Annual Session of the American Academy of Ophthalmology and Otolaryngology, Oct. 11-16, 1959, Chicago.

tration, different size probes may be used. In this case, a no. 3 and a no. 2 Bowman probe were used, incorporating a 3-0 and 4-0 silk suture, respectively. It was found difficult to make probes smaller than no. 2 by this method as the hammered plate became too thin and would break off. However, I am assured by the manufacturers of atraumatic needles that any size can be made when techniques similar to those used in making atraumatic needles are employed.

The instrument is passed through the lacrimal passages to the floor of the nose in the usual manner, under general anesthesia in the case of children. Once it has been identified, either under direct vision or by feel with another probe in the inferior meatus, it is grasped with a small forceps. It should be grasped as close to the end as possible, and this is accomplished by pulling it back slightly. It is then pulled out through the nose. This precaution minimizes the trauma to the mucous membrane of the nose by the tip of the probe. The mucous membrane can be shrunk down first for better visibility and easier manipulation, but this is not absolutely necessary since no worse damage can result than the possible loss of a small amount of mucous membrane with attending slight but insignificant bleeding.

After the probe has been pulled out through the nose, the terminal portion of the suture is cut off, and the ends are tied and taped to the face (fig. 2). Since the original suture is about 12 inches long, the remaining portion can be used several more times. The suture is left in place from several days to several months, depending on the subsidence of symptoms and the site and degree of obstruction. It is usually moved slightly once or twice a week to keep it from becoming fixed and to encourage canalization. When ready to remove, the suture is cut close to the punctum and pulled out through the nose.

FIGURE 2.

SUMMARY

A new instrument has been presented which facilitates threading the lacrimal passages in the repair of a laceration of the canaliculus and in the nonsurgical treatment of chronic obstruction of the nasolacrimal duct, especially in children. By employing this technique after two or three unsuccessful probings, a dacryocystorhinostomy was found to be unnecessary in these children. It offers the following advantages over other similar methods:

1. By using the desired size standard Bowman probes, it is possible to thread a suture into the lacrimal passages of even the smallest child.

2. A solid probe in the inferior meatus is easier to identify and grasp than other softer materials, thus assuring greater probability of success in the procedure.

3. The soft silk (or nylon) is better tolerated by the tissues, the patient is more comfortable, and it is easier to handle.

4. Being softer than either plastic tubing or dermal suture, it has less tendency to cut through the punctum or canaliculus, even when taped on the cheek instead of the forehead.

5. If necessary, one can replace a large suture with a smaller one, if there is doubt of the patency of the duct, by fusing the unraveled ends of the sutures and pulling the smaller one through.

The only disadvantages are (1) that care must be taken in extracting larger probes by exerting a slow steady pull, lest the punctum or canaliculus be damaged (the manufactured probes will be softer in the larger sizes), and (2) that there may be some trauma to the mucous membrane of the nose with minimal but inconsequential bleeding. Some familiarity with the normal anatomy of the nose will make the procedure easier to perform.

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3. ———: The Lacrimal System, New York, Grune & Stratton, 1955.

In Memoriam

Frank Barber.....Lima, New York
October 26, 1959

Wilbur Max Brown.....Mansfield, Ohio
December 4, 1959

Thomas M. Goodwin.....Elkins, West Virginia
October 17, 1959

Robert F. Loughmiller.....Oklahoma City, Oklahoma
September 22, 1959

James Homer McCready.....Pittsburgh, Pennsylvania
September 28, 1959

Bertha S. McDavitt.....Fort Worth, Texas
October 23, 1959

Prof. Dr. F. Nager.....Zurich, Switzerland
September 7, 1959

Donald O'Rourke.....Denver, Colorado
December 27, 1959

Philip Romonek.....Beverly Hills, California

Harry A. Rubenstein.....Syracuse, New York
October 2, 1959

Elbert S. Sherman.....Newark, New Jersey
September 11, 1959

Frank C. Sternes.....Cicero, Illinois
June 26, 1959

TRANSACTIONS

American Academy of Ophthalmology and Otolaryngology

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William L. Benedict, M.D., LL.D., Executive Secretary-Treasurer
American Academy of Ophthalmology and Otolaryngology
15 Second Street S.W., Rochester, Minnesota

CLINICS IN MEXICO — 1959

Following the meeting of the Sixty-Fourth Scientific Assembly of the Academy in Chicago and while the President of Mexico was on a good will tour of the United States, some seventy ophthalmologists, otolaryngologists and their wives made a tour into Mexico.

The Mexico City Session of the American Academy of Ophthalmology and Otolaryngology extended from October 17 to October 24. These meetings consisted of papers and demonstrations of work in the fields of ophthalmology, otolaryngology and plastic surgery.

In opening the meeting, Dr. William L. Benedict, Executive Secretary-Treasurer, expressed in the name of American ophthalmologists and otolaryngologists our gratitude to our Mexican colleagues for the privilege of meeting with them in this third post-convention tour to Mexico.

On October 19, the ophthalmologists and otolaryngologists made a tour of the Ophthalmology and Otolaryngology Departments of the Hospital General of Mexico City. Scientific discussion included:

1. New Technique in Ptosis Surgery (a motion picture)—Dr. Robert A. Schimek, New Orleans.
2. Treatment of Paralysis of the Bilateral Abductors of the Larynx—Dr. Ricardo Tapia, Mexico City.
3. Biomicroscopy in Retinal Detachment: Its Application in the Preoperative and Postoperative Stages—Dr. Juan Heatley, Mexico City.
4. Explanation of Teaching Ophthalmology to Graduates at the National University of Mexico — Dr. Magin Puig Solanes, Mexico City.

The ophthalmologists and otolaryngologists divided into small observation groups. The ophthalmologists saw patients with active cysticerus, filaria, and Vogt-Koyanagi syndrome. This included a pathological conference. Operative techniques for cysticerus not mentioned in standard American textbooks were

described. The otolaryngologists observed a rhinoplasty and a laryngeal operation.

On October 20, Drs. Antonio Torres Estrada and Arturo Chavira, Past President and Vice-President of the Pan-American Association of Ophthalmology, presided over a meeting of the Association for the Prevention of Blindness.

Dr. A. Benedict Rizzuti of Brooklyn, New York, gave an excellent paper on the use of preserved cornea in keratoplasty. He outlined in detail the indications for its use and answered many questions regarding details of his technique.

Dr. Luis Sanchez Bulnes of Mexico City showed a new technique of scleral buckling which he has used on some thirty cases. In brief, this consisted of making oval scleral resections with the long axis perpendicular to the limbus. The center of the resection corresponded when possible to the tears. The resections were usually 3 to 5 mm. wide and 5 to 6 mm. long. A barrage of diathermy connected them. Single interrupted mattress sutures closed the oval resections and created a fold over the area of holes. Fluid was drained from the areas of scleral resection. Tying of the sutures created a fold parallel to the limbus. Many unusual clinical cases were presented in a motion picture.

The otolaryngologists were divided into small groups and watched surgical procedures. They were impressed especially with the fine surgery of the ear and the larynx.

On October 21, a visit was made to the Children's Hospital, where on the wards four cases of retinoblastoma in various stages were seen. In addition, another ocular tumor of unknown etiology was seen. Prior to biopsy it was felt that this tumor arose in the ethmoid area. Dr. Feliciano Palomino Dena reviewed his experiences combining surgery, medication and chemotherapy in his sixty-two most recent cases of retinoblastoma. He compared these results with 100 eyes reviewed in 1954.

Dr. Graciela Navarro showed clinical cases in the strabismus and pleoptics clinic. Equipment was the most modern.

Dr. Ramon del Villar reviewed the management of five cases of nasopharyngeal fibroma.

Miss Barbara M. Simmons gave a fine paper entitled "Management of Heterophoria in the Young Child." She reviewed 104 cases in various age groups. She felt that the orthoptist should assist in the diagnosis as well as the therapeutics of heterophoria. (Her complete talk will be published at a later date in the American Orthoptic Journal.)

A very complete clinical and pathological study of generalized moniliasis with orbital localization was given by Dr. Feliciano Palomino Dena. Clinical impression prior to death and five days later was that this was probably a reticulosarcoma. It was pointed out that the early diagnosis of moniliasis can be difficult in that Monilia can be found often in the mouth and other areas.

In rhinoplastic surgery, it can be said that, in general, the accepted principle among our Mexican colleagues is never to do in one stage what they can do in two stages. This is in contrast to policies too frequently observed in the United States, where because of cost of rehospitalization and other factors, one-stage surgical procedures seem more the rule.

The social program of this post-convention tour included a bull fight, a city tour, a visit to the pyramids and to the famous church of Guadalupe. A "thank

you" dinner was given to our Mexican colleagues. Ever unforgettable will be the visit to University City, the lunch and farewell dinner at the Hotel Rancho Telva in Taxco, and the all too brief stay at the Hacienda Vista Hermosa with its beautiful pool.

To Dr. William Benedict and his staff we all owe a deep vote of thanks for making possible this third Mexico City session. We are equally thankful to our colleagues in Mexico City, who were most gracious in demonstrating unusual and instructive cases in their hospitals and clinics.

R. M. Fasanella, M.D.

HOME STUDY COURSES

The 1960-1961 Home Study Courses in Ophthalmology and Otolaryngology will begin on September 1 and continue for a period of ten months.

The emphasis in these courses is on the basic sciences related to the two specialties. Their wide acceptance over a period of 20 years is evidence of their value as a supplement to other training available to the young physician who is preparing to practice Ophthalmology or Otolaryngology. They are also a stimulating reading guide for the physician who is already practicing one of the specialties.

The faculties include members of the American Boards and of the staffs of many leading teaching institutions throughout the country, who are thoroughly conversant with available postgraduate training programs, and can evaluate the areas in which there is a maximum need for supplemental training.

The Home Study Courses are recommended by the American Board of Ophthalmology and the American Board of Otolaryngology, and by the directors of most residency programs.

Detailed information and application forms may be secured from Dr. William L. Benedict, 15 Second Street S.W., Rochester, Minnesota. Registration should be completed before August 15.

OTOTOXICITY OF DRUGS

The Committee on the Conservation of Hearing is interested in the ototoxicity of certain new drugs, including antibiotics. In many instances these drugs are introduced without previous knowledge of their possible toxic effect on hearing and it is only by the accumulation of specific case reports that the danger to hearing becomes known. An example is dihydrostreptomycin. Largely because of the article published under the sponsorship of the Committee on the Conservation of Hearing in the Journal of the American Medical Association for August 1959, the Federal Food and Drug Administration has prohibited the inclusion of dihydrostreptomycin in commercial "shotgun" preparations with penicillin.

In order to collect data on this and other drugs, especially antibiotics, which may have unsuspected toxic effects on the hearing, the members of the Academy are urged to submit case reports to the Academy for the Subcommittee on Research of the Committee on the Conservation of Hearing.

AWARDS FOR ORIGINAL INVESTIGATION IN OTOLARYNGOLOGY

Each year the American Academy of Ophthalmology and Otolaryngology offers awards for outstanding investigative work performed during residency training. These awards are an expression of the high value which the American Academy of Ophthalmology and Otolaryngology places on original effort as the basis of medical progress.

The main purpose of the awards is to give recognition for outstanding investigations performed by young physicians who have focused their attention on Otolaryngology. The Academy also hopes that the award program will provide an extra stimulus for those who have investigative ideas as well as a stimulus to department heads to provide time and facilities so that their students can pursue these ideas.

Separate awards will be given for clinical and for basic investigations in the broad field of Otolaryngology. The broad field of Otolaryngology includes the ear, nose, throat, nasopharynx, oral cavity, larynx, esophagus, tracheobronchial tree and neck. Clinical investigation is understood to mean any study involving human patients which contributes information regarding the symptomatology, etiology, diagnosis, course, complications, therapy, etc., of any otolaryngological disorder. Basic investigation includes any study which involves histologic, physiologic, audiologic, experimental-surgical and other similar procedures or lines of investigation. Research may be both of the clinical and basic types, such as a study involving both humans and animals, and the Awards Committee will decide in which category such a manuscript is to be considered.

The competition is open to Doctors of Medicine who have completed at least one year of internship (not necessarily in the United States or Canada) and who began resident training in Otolaryngology no longer than five years past. Residency training must be in an approved American or Canadian hospital but the contestant need not be an American or Canadian citizen. The investigative work must have begun during the normal three or four year residency program but may be completed afterward. The majority of the investigative work must have been performed by the contestant, although he may acquire needed advice and technical assistance. The work need not be entirely original and may represent a continuation of research already in progress in a laboratory. The author's name should appear on the title page. Co-authors may be listed, but the contestant must be the first author. When an equal contribution to the investigation has been made by two or more qualified contestants, a letter should accompany the manuscript stating this fact. A cash award made for an entry having two or more qualified authors will be divided equally between these authors.

The Academy wishes to allow the contestant complete freedom in the publication of the manuscript. Thus, both published and unpublished papers will receive equal attention so long as they are submitted within the time limitations indicated. Reprints will be accepted, if submitted within one year of publication. Manuscripts must be typewritten and follow accepted style for journal publication. An accompanying letter should state whether the manuscript

has been published or has been submitted for publication.

Judgments of merit will be based on scientific content as well as the manner of presentation. Manuscripts should contain a minimum of historical detail, review of the literature and statements of opinion.

The manuscripts must be in the hands of Dr. Juergen Tonndorf, University Hospitals, Iowa City, Iowa, not later than January 1, 1961 for awards to be presented in October 1961.

Awards will be made at the discretion of the Committee on Research and Finance of the Council of the American Academy of Ophthalmology and Otolaryngology and may be withheld if there are no manuscripts of merit. Cash awards shall not exceed six in number and shall not total more than $5000.00 in any one year. The award may be made for either clinical or basic research. Certificates of Merit may be awarded for exceptional manuscripts not winning cash awards. Letters in support of manuscripts will not be accepted by the Awards Subcommittee.

HAROLD F. SCHUKNECHT, M.D.
Chairman
Committee for Research in Otolaryngology
American Academy of Ophthalmology and Otolaryngology

HEARING TESTS

The Committee on Conservation of Hearing will conduct hearing tests during the week of the Annual Meeting. Three soundproof booths will be placed in the registration area and will be manned by technicians selected by the Committee. It is proposed to test the hearing of as many of the doctors attending the meeting as possible. An audiogram will be given the person so tested.

LISTING OF AUDIOMETERS

The following audiometers are recommended for listing as of December 15, 1959:

PURE TONE AUDIOMETERS

Abatron D100	Abatron Inc. P. O. Box 593 Whittier, California
Beltone Model 10-C Model 15-C	Beltone Hearing Aid Company Audiometer Division 2900 West 36th Street Chicago 32, Illinois
Maico Model MA-5 Model H1-B for pure tones only	Maico Electronics Inc. Maico Building 21 North Third Street Minneapolis 1, Minnesota
Sonotone Model 91	Sonotone Corporation Elmsford, New York

SPEECH AUDIOMETERS

Grayson-Stadler Model 162	Grayson-Stadler Co. West Concord, Massachusetts

LIMITED FREQUENCY AUDIOMETERS

Ambco OTO-CHEK 800	Ambco Inc. 1222 W. Washington Blvd. Los Angeles 7, California

SCREENING AUDIOMETERS

Ambco Otometer 600	Ambco Inc. 1222 W. Washington Blvd. Los Angeles 7, California

Each model number in the list as a rule indicates the most advanced model of that series. If less advanced instruments are for sale under similar model numbers, it is assumed that they will function as well or better than the more complicated model in a series.

Acceptance for listing means that the audiometer manufacturer has demonstrated the ability to produce one instrument that performs according to A.S.A. specification. It does not imply that any individual instrument will perform within the tolerances. It is obviously beyond the scope of the Listing Committee or the Referee Laboratories to provide production control for audiometer manufacturers and their customers; however, listing does indicate that the product of the manufacturer can come up to 1951 A.S.A. specifications, and it is up to the customer to carry on negotiation with the manufacturer if a particular instrument which he receives is faulty.

Abstracted from the 1959 Report of the Listing of Audiometers Subcommittee of the American Academy of Ophthalmology and Otolaryngology Committee on Conservation of Hearing.

THE INTERNATIONAL ASSOCIATION OF SECRETARIES OF OPHTHALMOLOGICAL AND OTOLARYNGOLOGICAL SOCIETIES

Minutes of the Annual Meeting

October 13, 1959

COUNCIL MEETING

The Council of The International Association of Secretaries of Ophthalmological and Otolaryngological Societies held a luncheon meeting on October 12, the day before the Annual Business Meeting. Those present were: President Roland H. Myers, President-Elect Michael H. Barone, Editor Paul C. Craig, Executive Board Members Daniel S. DeStio, Archie E. Cruthirds and Peter N. Pastore, Secretary J. David Stratton. Committee members Edley H. Jones and Roderick Macdonald were present to render a report. Benjamin F. Souders of Reading, Pennsylvania, and Ernest I. Glenister of Halifax, Nova Scotia, were present as invited guests.

The actions of the Council were presented to the Association at the Annual Meeting on October 13, and are included in the Minutes below.

ANNUAL MEETING

The Annual Meeting of the Association was held in Private Dining Room 14, Palmer House, at 5:30 p.m., October 13, 1959. The Association members were guests of the Academy at a dinner meeting, thirty-one persons being present. At the conclusion of the meal all present introduced themselves. The registration book was also signed by each. President Myers publicly welcomed Alejandro Salleras of Buenos Aires, Argentina, the only Cooperative Director attending the meeting.

With President Roland Myers presiding, it was moved and passed that the reading of the Minutes of the previous meeting be omitted and that they be approved as printed.

Ben Souders of Reading, Pennsylvania, was introduced by Editor Paul Craig and gave a detailed report, documented with folders and several slides, outlining the public relations program of the Pennsylvania Academy of Ophthalmology and Otolaryngology. He reported that the program had been of benefit in reaching the physicians of the state.

Edley Jones, Chairman of the Committee for Academy Liaison, gave a report concerning the activity of his committee. Due to some misunderstanding, we were not this year distributing survey report cards on the Academy Courses, but the Secretaries for Instruction had indicated to him that they did wish us to continue this practice. This year, letters will be sent to each secretary asking him to poll his members who attended the Academy meeting this year, and solicit their opinions concerning the courses taken. Dr. Jones reported that the Council had voted to continue the survey as long as the Academy wished us to do so.

Edley Jones also reported back concerning a letter which the Secretary had presented to the Council. The letter was from the Secretary of the Section on Ophthalmology of the American Medical Association asking the Association to compile a list of ophthalmologists for the Index Ophthalmologicus. His committee consulted with several persons who had some previous knowledge of

the matter and recommended that the Section be informed that we felt this was not a matter for us to handle.

The committee report was accepted.

The Financial Report was submitted by the Secretary, and copies distributed. The Auditing Committee reported the books to be in order. The Committee consisted of Drs. Lockhart, Craig, and Goff, who had been appointed by President Myers at the Council Meeting.

President Myers called on Archie Cruthirds to report for the International Relations Committee. Dr. Cruthirds discussed the founding of the Asia-Pacific Academy of Ophthalmology (see TRANSACTIONS, 63:115, Jan.-Feb. 1959) and urged us to support it in any way possible. He feels that a closer bond of professional societies will help in bettering international relations.

Dr. Cruthirds also reminded us of the XIX International Congress of Ophthalmology, which will meet in New Delhi, India, December 3-7, 1962. Cooperative Director Kiran Sen has been appointed President of the Congress. Dr. Cruthirds recommended that any member of the Association who goes to an overseas country be delegated as a representative of the Association.

The report was accepted.

Dan DeStio made a brief report about the status of the handbook which he has been preparing. It will be called "Helpful Hints to Secretaries" and has been completed. A draft was passed around to be seen by all. It will be published in the TRANSACTIONS of the Academy, after which reprints will be available. He reported that the Council at its meeting the day before had authorized the Secretary to obtain enough to have a five-year supply.

Paul Craig was recognized and read a Resolution concerning Moacyr E. Alvaro, Active Director, whose death occurred this summer. He moved that the Resolution be submitted for publication in the Academy TRANSACTIONS and that a copy be sent to Mrs. Alvaro. This was seconded and passed. President Myers then asked those present to stand in silent prayer in memory of Moacyr.

Dr. Craig also reported on the visit to this country by Professor Hi Joon Kim of Korea. Dr. Craig thanked and praised those who had welcomed Professor Kim into their homes, offices, and institutions, thus making a pleasant impression on the visitor.

The Nominating Committee report was made by Roderick Macdonald. Other members were Edley Jones and Dan DeStio. Dr. Macdonald submitted the following slate: President, Michael H. Barone; President-Elect, Peter N. Pastore; Editor, Paul C. Craig; Active Directors (for 3 years), F. E. Murdock to succeed himself, and Ernest I. Glenister to succeed R. J. Viger of Montreal. Dr. Macdonald moved the election of these men, and also moved that the Nominating Committee and officers be empowered to elect Cooperative Directors after further study, since time to consider names had been too short. This motion was seconded and passed unanimously.

There being no new business, after a short summation of his impressions of his year in office, and having thanked everyone for their help, retiring President Myers recognized the new President, Michael Barone. Dr. Barone said a few words of appreciation to the Association members, asking their help in the year to come.

There being no further business, the meeting adjourned.

J. DAVID STRATTON
Secretary

BOOK REVIEWS

PHYSIOLOGY OF THE EYE: CLINICAL APPLICATION. By Francis Heed Adler, M.A., M.D., F.A.C.S., Professor of Ophthalmology, University of Pennsylvania School of Medicine. Third Edition, St. Louis, C. V. Mosby Co., 1959. Cloth; 780 pp. plus index; 372 illustrations (2 in color). $16.00.

A standard medical textbook used in most schools and hospitals since the first edition appeared in 1950, Doctor Adler's Physiology of the Eye is a comprehensive and reliable repository of experimental and clinical data on one of the rapidly progressing fields of science in the medical curriculum. The arrangement of subject matter in chapters is based on anatomical areas and related functions. The commentary on laboratory findings and the evaluation of clinical observations that appear on each subject guides the reader in understanding some unusual and unfamiliar trends in interpretation of the application of new theories.

Changes in our conceptions of the aqueous are rapidly reflected in glaucoma as well as in responses to therapy for uveal disease. Tonography and tonometry have contributed to clinical diagnosis and treatment of glaucoma and current literature is replete with reports of series of cases that either refute, confuse or confirm conclusions of others. A deliberative consideration of the present status of research and examinations of patients is a welcome relief to the pangs of uncertainty that beset the casual reader.

The chapters on Ocular Motility and Accommodation are classic examples of the author's pre-eminence in these subjects, and there seems to be nothing omitted in the present edition. Electromyography and electroretinography are relatively new and unfamiliar topics but are reasonably covered. This is a book written by a teacher of ophthalmology for advanced ophthalmologists whether engaged in a study of a basic science or private practice.

W.L.B.

SYMPOSIUM ON GLAUCOMA. Edited by William B. Clark, M.D., St. Louis, C. V. Mosby Co., 1959. Cloth; 300 pp.; 99 figures, including two in color; complete index. $13.50.

A Symposium on Glaucoma was sponsored by the New Orleans Academy of Ophthalmology in its 1957 Annual Meeting. The panelists were chosen because of their specialized interest in particular phases of glaucoma; its histology, pathology, biochemistry, diagnosis and treatment ". . . and their contributions cover the latest concepts of the disease of glaucoma and the most modern techniques of the management." All of the eight panelists have done extensive research in glaucoma, most of which has been reported in previous works, and are eminently fitted to teach the subject. In this volume the editor has compiled the formal lectures given on the symposium and, in addition, a lengthy spontaneous forum in which questions from the audience are answered by the panelists, which contributes to the fuller understanding of glaucoma and what is being done about it. This volume is a source of information and an aid in teaching which should be a desk book in the office of every clinician who sees patients with

glaucoma whether he be an ophthalmologist or a general practitioner. The New Orleans Academy of Ophthalmology has done a worthy service in making this information available.

W.L.B.

EDUCATION AND HEALTH OF THE PARTIALLY SEEING CHILD. By Winifred Hathaway. Revised by Franklin Foote, M.D., Dorothy Bryan and Helen Gibbons. Fourth Edition, New York, Columbia University Press for the National Society for the Prevention of Blindness, Inc., 1959. 169 pp.; 27 illustrations; 14 figures; appendices, bibliography, indices. $5.00.

In all public and private schools the pupils and students are now carefully screened for physical and mental disabilities that may handicap them in learning. In recent years there has been increasing attention to lighting of schoolrooms and positioning of pupils near and remote from windows to enable the best conditions for seeing. For it is estimated that 80 per cent of a child's learning is acquired through vision, and any visual disability is a handicap to learning in proportion to its severity.

In public city schools, visually handicapped children are provided with books, blocks, blackboards and charts with large letters or figures in well lighted rooms and are segregated from pupils with normal vision. In rural schools the special attention to partially blind pupils must be solved in another way.

Mrs. Hathaway pioneered in special instruction for partially blind pupils and was instrumental in establishing classes and training courses in a number of university and normal schools. Out of her experience this book has been compiled and revised.

Written for teachers, parents and school officials, it describes the best known method of preschool screening, selection, teaching and counseling the partially blind child. There are chapters on Community Relationships and Educational Procedures that should be studied in every P.T.A. and in teachers' work shops.

W.L.B.

GEOGRAPHIC OPHTHALMOLOGY: ASIA, AUSTRALIA AND AFRICA. By twenty authors. Edited by William John Holmes, M.D., Springfield, Ill., Charles C Thomas, 1959. Cloth; 312 pp.; 132 illustrations. $8.50.

The preface of this book explains that no attempt is made to include all the major eye diseases of the continents named in the title. A major contribution is the description of the many cultural, social, and public health factors influencing the eye diseases prevalent in Asia, Australia and Africa. Some of the twenty contributing authors relate with clarity the living conditions of the people as they affect eye disease, its distribution, diagnosis and treatment.

The specific diseases discussed include malaria, leprosy, onchocerciasis, trachoma, chronic nontrachomatous follicular conjunctivitis, phlyctenular ophthalmia, xerophthalmia and keratomalacia, pterygium, solar chorioretinal burn, and orbital rodent ulcers.

Other chapters are devoted to the treatment of corneal ulcers, surgery for westernizing the oriental eye, radiotherapy of pterygium, anterior chamber surgery, corneal surgery for refractive errors, penetrating keratoplasty, cataract surgery as an office procedure, and the

Smith-Indian cataract extraction with present-day modifications.

Much of the material presented is not new, but it is a worthwhile review, particularly for those of us who seldom see tropical diseases. The descriptive picture of the diseases and the people is worth the reading of the book. Some of the authors relate their own experience or viewpoint, which always adds interest to the reading.

The authors and editor have written a readable book. The material presented is good and seems to be given as a challenge or stimulus to the ophthalmologist. This challenge is expressed in the opening chapter for closer communication in disseminating known facts of eye disease and a stimulus to closer co-operation for research on world-wide eye disease. It implies to the reviewer that our world is smaller, our contact with others is increasing, and our knowledge and research must expand.

T.J.K.

SPEECH CORRECTION AT HOME. By Morris V. Jones, Ph.D. Springfield, Ill., Charles C Thomas, 1957. Cloth; 138 pp., 52 illustrations. $4.75.

An increasing interest of the otologist in hearing problems has made him more aware of the secondary speech difficulties that accompany such disorders, especially in children. The laryngologist has become interested in esophageal speech. Patients and their parents expect the otolaryngologist to understand these problems and direct them to proper sources for their solutions.

This book gives a rapid nontechnical survey of these difficulties and the ways to meet them. It would also furnish useful information to an anxious mother. I believe that all otolaryngologists will find the book helpful.

H.L.W.

SYNOPSIS OF EAR, NOSE AND THROAT DISEASES. By Robert E Ryan, M.D.; William C. Thornell, M.D. and Hans von Leden, M.D., St. Louis, C. V Mosby Co., 1959. 383 pp. $6.75.

In this book the three authors have covered the field of otorhinology and laryngology with the succinctness called for in a synopsis, but also with an adequacy far beyond what its title suggests. Designed as a ready reference for the general practitioner, the medical student, the intern, the nurse, and the speech pathologist, it fully attains its goal. I think that it may be fairly compared to May's book on the eye, which has served such a useful purpose for so many years.

H.L.W.

SURGERY OF THE EAR. By George E. Shambaugh, Jr., Philadelphia, W. B. Saunders Co., 1959. 668 pp. $27.50.

Dr. Shambaugh has produced a book that no otologic surgeon, whatever his qualifications, can afford to be without.

While possibly lacking the literary artistry of Ballance's Suppuration of the Temporal Bone, it possesses the auctorial merit of clarity in an extreme degree. While Whiting and Ballance produced the outstanding books in English on otologic surgery of their eras, this present volume is fully worthy of standing with theirs and in due time will also receive the accolade of "classic."

H.L.W.

NEWS AND ANNOUNCEMENTS

AMERICAN OTOLOGICAL SOCIETY

Dr. Lawrence R. Boies, Secretary-Treasurer of The American Otological Society, Inc., has announced the following program for the annual meeting of the Society at The Deauville Hotel, Miami Beach, Fla., on March 13 and 14, 1960.

Sunday, March 13, 1960, 9:00 a.m.

1. Early Embryology of the Auditory Ossicles and Associated Structures in Relation to Certain Anomalies Observed Clinically by Barry J. Anson, Ph.D. (Med. Sc.); Jerome S. Hanson, M.D. (by invitation), and Shatik F. Richany, Ph.D., (by invitation).

2. Tissue Reaction Following Reconstruction of the Oval Window in Experimental Animals, by Richard J. Bellucci, M.D., and Dorothy Wolff, Ph.D., (by invitation).

3. Human Cochlear Responses to Sound Stimuli, by John L. Bordley, M.D.; Robert J. Ruben, A.B. (by invitation), and George R. Nager, M.D. (by invitation).

4. Some Physiological Factors in Inner Ear Deafness, by Merle Lawrence, Ph.D.

5. Distribution of Hearing Loss in Various Population Centers, by Aram Glorig, M.D.

Sunday, March 13, 1960, 2:00 p.m.

6. The Management of Middle Ear Lesions Simulating Otosclerosis, by Francis A. Sooy, M.D. (by invitation).

7. Experiences with the Stapedectomy Technique of Shea for the Surgical Treatment of Otosclerosis, by David Myers, M.D.; Woodrow D. Schlosser, M.D. (by invitation), and Richard A. Winchester, Ph.D. (by invitation).

8. Vein Plug Stapedoplasty, by Clair M. Kos, M.D.

9. Partial Stapedectomy, by J. V. Hough, M.D. (by invitation).

10. Experimental and Clinical Experiences in Oval Window Surgery, by Harold Schuknecht, M.D.

Open discussion of last four papers.

Monday, March 14, 1960, 9:00 a.m.

11. Acceleration as a Means of Determining the Sensitivity of the Components of the Non-Auditory Membranous Labyrinth, by Walter H. Johnson, Ph.D. (by invitation); J. Brydon Smith, M.D., and Joseph A. Sullivan, M.D.

12. Localization of Monaurally Impaired Listeners, by Richard Viehweg, M.A. (by invitation).

13. Deafness Due to Mumps: Inner Ear Pathology, by John R. Lindsay, M.D., and Patricia R. Davey, F.R.C.S. (Ed) (by invitation).

14. Action of Enzymes of Effusions Obtained from the Middle Ear, by Carl F. Gessert, Ph.D. (by invitation); Elizabeth S. Baumann (by invitation), and Ben Senturia, M.D.

15. Tumors of the Temporal Bone in Their Reciprocal Behavior, by George Kelemen, M.D.

Monday, March 14, 1960, 2:00 p.m.

16. Labyrinthectomy, by Terence Cawthorne, F.R.C.S.

17. The Lurking Latent Cholesteatoma, by Victor Goodhill, M.D.

The Profession is cordially invited to attend.

OKLAHOMA CITY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

The Sixth Annual Spring Meeting of the Oklahoma City Academy of Ophthalmology and Otolaryngology with the Postgraduate Department of the University of Oklahoma Medical Center will be held on March 3 and 4, 1960. Guest speakers will include the following ophthalmologists: Dr. Victor A. Byrnes, St. Petersburg, Fla., and Dr. Daniel Snydacker, Chicago. Otolaryngologists who have been invited to present papers are Dr. Wesley E. Compere, Jr., Los Angeles; Dr. G. O'Neil Proud, Kansas City, Kansas, and Dr. French K. Hansel, St. Louis.

For further information, write to E. Norris Robertson, Jr., M.D., 301 N. W. 12th St., Oklahoma City.

AMERICAN SOCIETY OF FACIAL PLASTIC SURGERY

Dr. Samuel M. Bloom, secretary of the American Society of Facial Plastic Surgery has announced the following meetings of the Society in 1960:

April 6
July 22
Hotel Elysee, 60 E. 54th St., New York
October 13
Chicago, Illinois

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY NORTH CAROLINA EYE, EAR, NOSE, AND THROAT SOCIETY

The 1960 joint meeting of the South Carolina Society of Ophthalmology and Otolaryngology and the North Carolina Eye, Ear, Nose, and Throat Society will be held at the King Cotton Hotel, Greensboro, North Carolina. The dates are September 12, 13, 14, 1960.

WEST VIRGINIA

The West Virginia Academy of Ophthalmology and Otolaryngology will hold its annual meeting at the Greenbrier Hotel, White Sulphur Springs, West Virginia, April 10 to 12, 1960.

Among the guest speakers will be Dr. Harold G. Scheie, Professor of Ophthalmology, Pennsylvania University School of Medicine, Philadelphia; Dr. Charles E. Iliff, Associate Professor of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore; and Dr. Oscar T. Becker, Clinical Associate Professor of Otolaryngology, University of Illinois, Chicago.

For any additional information please contact the secretary, Dr. Albert C. Esposito, First Huntington National Bank Bldg., Huntington 1, W. Va.

POSTGRADUATE COURSES

The Mount Sinai Hospital

An intensive Postgraduate Course in Rhinoplasty, Reconstructive Surgery of the Nasal Septum and Otoplasty will be given July 16 through July 29, 1960, by Dr. Irving B. Goldman and staff at the Mount Sinai Hospital in affiliation with Columbia University.

Candidates for the course should apply to the Registrar for Postgraduate Medical Instruction, The Mount Sinai Hospital, Fifth Avenue and 100th Street, New York 29.

Institute of Ophthalmology Of The Americas

A three-week intensive course in Ophthalmic Plastic Surgery will be conducted in New York April 25 through May 14, 1960.

The course will consist of lectures, sessions in doctors' offices, preliminary and follow-up cases that are operated on during the time of the course, motion picture demonstrations of various ophthalmic plastic procedures, observation and assistance at the operating table on actual surgical cases, cadaver work and lectures and demonstrations, ancillary subjects such as photography, pathology, x-ray and radiation.

Anyone interested should contact the Registrar of the Institute of Ophthalmology of the Americas, New York Eye and Ear Infirmary, 218 Second Ave., New York 3, or any of the following: Dr. Wendell L. Hughes, 131 Fulton Ave., Hempstead, N. Y.; Dr. Byron C. Smith, 722 Park Ave., New York 21; Dr. J. Gordon Cole, 780 Park Ave., New York 21.

The University of Michigan Medical School

Dr. John M. Sheldon, Director of the Department of Postgraduate Medicine, Head of the University of Michigan Medical School has announced the following dates for postgraduate conferences for ophthalmologists and otolaryngologists during 1960: Otolaryngology conference, April 21, 22 and 23; ophthalmology conference, April 25, 26 and 27. For further information write to Dr. John M. Sheldon, Room 1610, University Hospital, Ann Arbor, Michigan.

Chicago Ophthalmological Society

The Chicago Ophthalmological Society will hold its annual clinical conference on February 12 and 13, 1960, at the Drake Hotel in Chicago.

The guest speakers will include Dr.

Walter S. Atkinson, Watertown, N. Y.; Dr. Gilbert Baum, Port Chester, N. Y.; Dr. James Bennett, Cleveland; Dr. Paul Cibis, St. Louis; Dr. Robert Hollenhorst, Rochester, Minn.; Dr. Isaac Tassman, Philadelphia; Dr. Bertha A. Klien, Dr. Peter C. Kronfeld, Dr. Oscar Sugar, and Dr. Derrick T. Vail, Chicago.

The program will include a symposium on retinal disorders, and papers on ophthalmodynamometry in intracranial vascular disease, observation on cataract surgery, ultrasonography in clinical ophthalmology, photocoagulation of iris and retina, a new surgical approach to lacrimation problems, a neurosurgeon looks at ophthalmology, and ligament of Wieger.

The Sixteenth Annual Sanford R. Gifford Memorial Lecture will be delivered by Dr. Walter S. Atkinson of Watertown, N. Y., on Friday, February 12, 1960, at the Drake Hotel at 5:15 p.m. All ophthalmologists are invited to attend the Gifford Memorial Lecture and the dinner which follows.

Registration fee for the entire course, including round table luncheons and dinner following the Gifford Memorial Lecture, is $45.00 and is payable to the Registrar: Mrs. Edward J. Ryan, 1150 North Lorel Ave., Chicago 51.

UNIVERSITY OF CHICAGO

Dr. Albert M. Potts has been appointed professor of ophthalmology in the department of surgery and director of research in ophthalmology at the University of Chicago.

Dr. Potts has been a member of the faculty of Western Reserve University, Cleveland, since 1948. He was associate professor of ophthalmic research from 1954 to 1959.

A biochemist and a specialist in toxicology of the eye and in electrophysiology, Dr. Potts will conduct research in these areas at the University of Chicago in addition to his teaching and clinical duties.

During World War II, Dr. Potts served as associate biochemist with the U. S. Office of Scientific Research and Development from 1942 to 1944, and as biochemist with the Manhattan District Project, 1944 to 1945. He was an assistant in biochemistry at the University of Chicago, 1938 to 1942.

Dr. Potts received his Bachelor of Arts degree in chemistry from Johns Hopkins University in 1934, his Ph.D. in biochemistry from the University of Chicago in 1938, and his degree as Doctor of Medicine from Western Reserve University in 1948. He is the author of more than sixty articles on biochemical and ophthalmologic research. He has been certified by the American Board of Ophthalmology and is a member of the American Academy of Ophthalmology and Otolaryngology, the Association for Research in Ophthalmology, and the American Chemical Society.

WILLIAM BEAUMONT HOSPITAL, ROYAL OAK, MICHIGAN

Dr. Herman D. Scarney, Assistant Clinical Professor of Ophthalmology in Wayne University Medical School, and Chief of Staff of William Beaumont Hospital, Royal Oak, Michigan, was placed on the retired list of the United States Navy Reserve with the rank of Rear Admiral as of September 1, 1959.

Admiral Scarney completed over 30 years of service in the United States Navy and was active in the aviation arm of the Navy during World War II. He spent five and one-half years on active duty serving as Senior Medical Officer and Chief Flight Surgeon at the Naval Air Station, Grosse Ile, Michigan; Naval Air Station, Dallas, Texas, and Senior Medical Officer and Chief Flight Surgeon on the Staff of the Commanding General, U. S. Marine Air Station, Cherry Point, N. C. He served as Senior Medical Officer and Chief Flight Surgeon aboard the Aircraft Carrier U. S. S. Cabot operating with the Third and Fifth Fleets under the commands of Admiral William Halsey and Admiral Spruance.

Admiral Scarney is authorized to wear four compaign stars for action in the China Sea, Manila, Iwo Jima, Tokyo and Okinawa. For participation in the Battle of Leyte, Admiral Scarney was awarded the Bronze Star with Combat "V" for heroic services while under immediate attack off the Philippine Islands.

Admiral Scarney is Past President of the Detroit Ophthalmological Society; Life Fellow of the American Academy of Ophthalmology and Otolaryngology; Fellow of the American College of Surgeons, and a Diplomate of the American Board of Ophthalmology.

POSITIONS AVAILABLE

WANTED—Ophthalmologist, Board-certified or qualified, not over 35. To join a five-man group of ophthalmologists in San Francisco. California license required. Commencing at a salary, but with possibility of future partnership. For further information write Albert A. Steiner, M.D., 1801 Bush St., San Francisco.

EYE, EAR, NOSE and THROAT practice for sale in Beverly Hills, Calif. Well established and fully equipped modern office. Excellent location. Available immediately due to recent death of physician. Terms open. For information write to Mrs. Philip L. Romonek, 405 N. Bedford Drive, Beverly Hills, Calif.

E. E. N. T. practice for sale. Well equipped office of ophthalmic surgeon and E. E. N. T. physician in city of 45,000. For information, write Mrs. W. Max Brown, 1010 Millsboro Road, Mansfield, Ohio.

Facilities for Ophthalmologist or E. E. N. T. man to share a two-man clinic, located in Lake Geneva, Wis. Lake Geneva is located in Walworth County, which has a population of over 50,000. No other E. N. T. man in the county, and one part-time ophthalmologist.

The opportunities for either an E. E. N. T. man or ophthalmologist are excellent. The new clinic building is now ready. The practice would be on a private basis.

Write for further information to E. D. Hudson, M.D., Hudson Clinic, Lake Geneva, Wis.

WANTED—at Temple University Medical Center, a scientist, either M.D. or Ph.D., trained in otologic research to direct a laboratory of otologic research at Temple University Medical Center. Inquiries should be directed to David Myers, M.D., Professor and Head of the Department of Otorhinology, Temple University Medical Center, Broad and Ontario Streets, Philadelphia 40.

An OPHTHALMOLOGIST is wanted to join a 12-man, modern clinic encompassing the majority of the medical specialties and serving a population of approximately 50,000. For further information write H. M. Blair, M.D., Administrative Director, Sault Polyclinic, Sault Ste. Marie, Mich.

OPHTHALMIC OFFICE AVAILABLE. Easily accessible office in downtown Fort Lauderdale, Fla. Available for purchase of equipment, fixtures, and lease. For information write Garland M. Johnson, M.D., Blount Bldg., Fort Lauderdale, Fla.

AURAL SURGEON. Diplomate of both American Board of Ophthalmology and American Board of Otolaryngology wants partner, Board certified or Board eligible. Midwestern medical center; population, 60,000. For information write George C. Foster, M.D., 15 Broadway, Fargo, N. D.

Listings of positions available should be sent to W. L. Benedict, M.D., 15 Second Street S. W., Rochester, Minn., by the fifth of the month preceding publication. They should include (1) type of physician wanted (ophthalmologist or otolaryngologist: diplomate, resident, etc.) (2) type of position to be filled: and (3) to whom to write for further information. Unless otherwise requested, listings will be published only once.

The Academy will handle no further correspondence beyond the listing and assume no responsibility. Neither does it endorse nor guarantee any of the published listings.

FOREIGN SUBSCRIPTIONS

Some foreign members of the Academy as well as subscribers to the TRANSACTIONS are experiencing difficulty in remitting in American dollars. For their convenience the Academy will accept any legal foreign currency in payment of dues, fees for Home Study Courses, Teachers' Manuals, Orthoptic Journals, TRANSACTIONS, etc., at the prevailing rate of currency exchange.

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